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McNeil

McNEIL CONSUMER HEALTHCARE, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034 (215) 273-7000

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane (Room #1061)
Rockville, MD 20857

FEB 1 1999

RE: Docket 77N-0094
Citizen Petition to Amend the Tentative Final Monograph for Internal Analgestic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Use – Expanded Age Groups for OTC Consumer Dosing Instructions covering Acetaminophen

Dear Sir/Madam:

McNeil Consumer Healthcare submits this citizen petition under 21 CFR 10.30 and 330.10 to request that the Commissioner of Food and Drugs amend the Tentative Final Monograph for Over-the-Counter Internal Analgestic, Antipyretic and Antirheumatic Drug Products to expand the pediatric age groups for OTC consumer dosing instructions covering acetaminophen. For concentrated drops products for infants, this would include expanded dosing instructions for children two months to less than two years of age. For less concentrated liquids, it would include expanded dosing instructions for children four months to less than two years of age.

Acetaminophen has been marketed in OTC dosage forms (infants' drops and children's elixir) since 1959 and there is wide recognition of its well established safety and effectiveness in the pediatric population. In 1983, McNeil, on its own initiative, developed acetaminophen dosing schedules for health care professionals to supplement the labeling instructions as published in the 1977 proposed rule. Dosing schedules for appropriate use of acetaminophen in children based on age and weight were developed. These schedules were designed to more closely correlate with the administration of acetaminophen in the effective dose range of 10 to 15 mg/kg of body weight per single dose and included directions down to 0-3 months of age for infants' drops and 4-11 months of age for children's liquids. These schedules were made available to health care professionals through the Physician's Desk Reference (PDR) and through professional materials. Thus, professional dosage schedules for acetaminophen products have been in use for approximately 15 years and it is recognized that physicians frequently recommend to consumers the use of pediatric acetaminophen in children less than two years of age.

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Additionally, FDA has held two meetings (January 13, 1995; September 18, 1997) of the Nonprescription Drugs Advisory Committee (NDAC) to discuss pediatric labeling, dosages and dosage forms. During the September 18th meeting, NDAC concluded that the age limit for OTC pediatric analgesics/antipyretics could be lowered to under two years of age (possibly down to 2 months of age) and that such dosing information could be included with the OTC labeling. No action, however, has been taken on the recommendations coming out of that meeting.

As shown in the attached petition, McNeil believes that 39 years of OTC marketing experience with pediatric acetaminophen fulfills the requirements outlined in 21 CFR 330.10 (4)(i) and (ii) regarding general recognition of safety and effectiveness and it has been used "to a material extent" and "for a material time" with a well established record of safety and efficacy in children. As such, the OTC dosing instructions should be expanded to provide consumers with information including children under two years of age.

If there are any questions or comments on this submission, please contact me at 215-273-7878.

Very truly yours,
McNEIL CONSUMER HEALTHCARE

Paula J. Oliver

Paula J. Oliver
Senior Director
Regulatory Compliance

cc: Debra Bowen, MD (HFD-560)
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CITIZEN PETITION

The undersigned, McNeil Consumer Healthcare, submits this petition under 21 C.F.R. 10.30 and 330.10 to request the Commissioner of Food and Drugs to take the following actions with respect to acetaminophen use in the pediatric population.

A. Action Requested

McNeil requests that the Commissioner, as authorized under 330.10(a)(7)(v) and 330.10(a)(12)(i), amend the directions for use covering pediatric acetaminophen products in the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use to expand the age groups for OTC consumer dosing instructions. For concentrated drops' products for infants, this would include expanded dosing instructions for children two months to less than two years of age. For less concentrated liquids, it would include expanding dosing instructions for children four months to less than two years of age. The TFM, as published in the *Federal Register* under proposed 21 CFR 343.50(d)(2), does not provide OTC dosing instructions for children under 2 years of age.

The proposed dosing schedule for children less than two years of age is shown in the following tables, along with currently approved dosing for children:

Recommended Pediatric Dosing of Acetaminophen By Weight and Age

Concentrated Drops (80 mg/dropperful)

WEIGHT	AGE	DOSE
Under 2 mos*		**Consult Doctor**
9-11 lbs	2-3 mos*	½ dropperful (0.4 mL)
12-17 lbs	4-11 mos	1 dropperful (0.8 mL)
18-23 lbs	12-23 mos	1 ½ dropperfuls (1.2 mL)
24-35 lbs	2-3 yrs	2 dropperfuls (1.6 mL)

*Always Call Doctor For Fever in Children Under Age 4 Months

Recommended Pediatric Dosing of Acetaminophen by Weight and Age

Liquids (160 mg/teaspoon)

WEIGHT (lb)	AGE (months/years)	DOSE (tsp)
Under 4 months		Consult Doctor
12-17 lbs	4-11 months	½ tsp
18-23 lbs	12-23 months	¾ tsp
24-35 lbs	2-3 yrs	1 tsp
36-47 lbs	4-5 yrs	1 ½ tsp
48-59 lbs	6-8 yrs	2 tsp
60-71 lbs	9-10 yrs	2 ½ tsp
72-95 lbs	11 yrs	3 tsp

Additionally, McNeil further requests that the Commissioner expeditiously publish an enforcement policy in the *Federal Register* to provide for labeling of pediatric acetaminophen products with expanded dosing instructions pending establishment under the OTC drug review of the final monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Drug Products.

B. Statement of Grounds

The Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use was published at 53 Fed. Reg. 46204 (November 16, 1988). McNeil wishes to amend the TFM to expand the directions for use covering acetaminophen so as to provide OTC consumer dosing instructions for children under 2 years of age.

Under 21 CFR 330.10(a)(7)(v), new data or information submitted to FDA more than 12 months after publication of a Tentative Final Monograph must be submitted as a petition to amend the monograph. Further, new data or information will be considered by the Commissioner only after a final monograph has been published in the *Federal Register* unless the Commissioner finds that good cause has been shown that warrants earlier consideration.

Good cause exists for consideration of this petition to amend the TFM before the final monograph is published, and, in the interim, to expeditiously publish an enforcement policy that would permit marketing of OTC pediatric acetaminophen products with labeling that contains expanded dosing instructions for consumers.

Acetaminophen has been marketed in OTC pediatric dosage forms (infants' drops and children's elixir) since 1959. In 1988, when the TFM was published, these pediatric dosage forms had already been marketed for 29 years. Now, these pediatric dosage forms have been available for 39 years and there is wide recognition of acetaminophen's well established safety and effectiveness in the pediatric population.

Eleven years passed between the publication of the proposed monograph for Internal Analgesic products in 1977 and the publication of TFM in 1988. Another eleven years have now passed without publication of a final monograph and the date for publication of the final monograph is uncertain.

Since 1983, a pediatric dosing schedule, using standardized age breaks consistent with FDA dosing schedules for OTC analgesics and with standardized weight ranges has been available [1]. This schedule provides doses for all pediatric age ranges, from neonate through age 11 years, and for comparable weight ranges. These age and weight schedules were designed to correlate with the administration of acetaminophen in the effective dose range of 10 to 15 mg/kg of body weight per single dose. McNeil, on its own initiative, has utilized this acetaminophen dosing schedule to give guidance to health care professionals, supplementing the labeling instructions in the 1977 proposed rule. McNeil has provided dosing directions down to 0-3 months of age for Infants' TYLENOL® Concentrated Drops and down to 4-11 months for Children's TYLENOL® Liquids. This information has been made available through the Physician's Desk Reference (Attachment 1) and through other professional materials (Attachment 2). The schedule proposed by Temple [1] has been widely accepted [2, 3, 4, 5, 6, 7, 8] in the pediatric medical community. As a result, professional dosage schedules for acetaminophen products have been in use for approximately 15 years and acetaminophen's well established safety and effectiveness in this young pediatric population is widely recognized.

Further, with regard to the issue of good cause, FDA has held two meetings of the Nonprescription Drugs Advisory Committee (NDAC) to discuss pediatric labeling, dosages and dosage forms. NDAC met on January 13, 1995 to discuss the issue of reconciliation of internal analgesic dosage schedules with those of other cough-cold ingredients for OTC pediatric combination products. NDAC met again on September 18, 1997 on the subject of the lower age limit for OTC acetaminophen and ibuprofen containing products. During the September 18, 1997 meeting, NDAC concluded that the age limit for OTC pediatric analgesics/antipyretics could be lowered to under two years of age (possibly down to 2 months of age) and that dosing information should appear on OTC labeling of pediatric analgesics. Also, the labeling could direct the consumer to consult a doctor concerning fever in the youngest children. However, over a year has passed since that meeting was held and no FDA action has been taken on recommendations coming out of that meeting.

The FDA Modernization Act of 1997 (Section 120) requires that within 90 days after a Scientific Advisory Panel makes a recommendation on a matter under its review, the agency must notify affected persons of (1) the final decision on the matter and the rationale therefore or (2) of the reasons that no decision has been reached. Although the NDAC meeting to discuss lowering the age limit for OTC pediatric analgesic/antipyretic products preceded the signing of FDAMA, the decisions that were reached at that meeting are important public health recommendations that should be promptly implemented, consistent with the spirit and intent of Section 120 of FDAMA. In addition, Section 111 of FDAMA encourages the development of pediatric indications for drugs, so they may be used appropriately in this population. The actions requested in this petition are consistent with the objectives of this important provision of FDAMA as well.

The primary benefit of treatment with an OTC antipyretic/analgesic is to provide symptomatic relief and comfort to the child. In the general practice of medicine, physicians commonly recommend to consumers the use of an OTC pediatric analgesic/antipyretic product in children less than two years of age. This is consistent with current medical opinion that control of fever provides significant benefit in the symptomatic management of young children. Adding consumer dosing instructions on the OTC product label for children under 2 years of age would also offer other important benefits. Consumers would have the correct information available on the label at every use of the product, which could then be used to validate the verbal dosing recommendations that are often provided by physicians or other health care providers; an extremely important consideration. Validation of this nature would minimize miscommunications between consumers and health care providers and could possibly reduce the occurrence of accidental misdosing in children.

With 39 years of OTC marketing history and widespread OTC use in the pediatric population, acetaminophen clearly has been used "to a material extent" and "for a material time". Professional acetaminophen dosing schedules for children under two years of age have been extensively used since 1983 and there is a well-established record of acetaminophen's safety and efficacy in children.

As the foregoing information points out, OTC acetaminophen use in children under two years of age is generally recognized as safe and effective. As such, the OTC dosing instructions should be expanded and added to the TFM for Internal Analgesic, Antipyretic and Antirheumatic Drug Products. In addition, since there is no definite date for publication of the final monograph, the agency should expeditiously publish an enforcement policy in the *Federal Register* that would provide for marketing of pediatric acetaminophen products that are labeled for consumers with expanded dosing instructions pending establishment of the final monograph.

C. Environmental Impact

McNeil does not believe that there would be an environmental impact resulting from FDA granting this petition. McNeil believes that the actions requested here qualify for a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.31(a) as an action on an OTC monograph that does not increase the use of the active moiety.

D. Economic Impact

A statement of economic impact will be provided if requested by the Commissioner pursuant to 21 CFR 10.30(b).

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition.

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ATTACHMENT 1

OTC PHYSICIANS' DESK REFERENCE

1985

McNeil Consumer—Cont.

administer to children under 12. Reduce dosage if nervousness or sleeplessness occurs. If you have high blood pressure, heart disease, diabetes, or thyroid disease or are presently taking a prescription drug for the treatment of high blood pressure or emotional disorders, do not take except under the advice and supervision of a physician. If symptoms persist for 7 days or are accompanied by high fever, consult a physician. **Do not use if carton is opened, or if printed red-neck wrap or printed foil inner seal is broken. Keep this and all medication out of the reach of children. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. In case of accidental overdosage, contact a physician or poison control center.**

Overdosage: Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In all cases of suspected overdose, immediately call your regional poison center or the Rocky Mountain Center's toll-free number (800-525-6115) for assistance in diagnosis and for directions in the use of N-acetylcysteine as an antidote, a use currently restricted to investigational status. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion. The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quanitity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals. The antidote, N-acetylcysteine, should be administered as early as possible, and within 16 hours of the overdose ingestion for optimal results. Following recovery, there are no residual structural or functional hepatic abnormalities.
Symptoms from pseudoephedrine overdose consist most often of mild anxiety, tachycardia and/or mild hypertension. Symptoms usually appear within 4 to 8 hours of ingestion and are transient, usually requiring no treatment.

How Supplied: Capsules (colored yellow and white imprinted "EXTRA-STRENGTH SINE-AID®")—tamper-resistant bottles of 20.

Shown in Product Identification Section, page 414

Children's TYLENOL® acetaminophen Chewable Tablets, Elixir, Drops

Description: Each Children's TYLENOL Chewable Tablet contains 80 mg. acetaminophen in a fruit flavored tablet. Children's TYLENOL acetaminophen Elixir is stable, cherry flavored, red in color and is alcohol free. Infants' TYLENOL Drops are stable, fruit flavored, orange in color and are alcohol free.
Children's TYLENOL Elixir: Each 5 ml. contains 160 mg. acetaminophen.
Infant's TYLENOL Drops: Each 0.8 ml. (one calibrated dropperful) contains 80 mg. acetaminophen.

Actions: TYLENOL acetaminophen is an effective antipyretic/analgesic. It produces antipyresis through action on the hypothalamic heat-regulating center and analgesia by elevation of the pain threshold.

Indications: Children's TYLENOL Chewable Tablets, Elixir and Drops are designed for treatment of infants and children with conditions requiring reduction of fever or relief of pain—such as mild upper respiratory infections (tonsillitis, common cold, "grippe"), headache, myalgia, post-immunization reactions, post-tonsillectomy discomfort and gastroenteritis. TYLENOL acetaminophen is useful as an analgesic and antipyretic in many bacterial or viral infections, such as bronchitis, pharyngitis, tracheobronchitis, sinusitis, pneumonia, otitis media, and cervical adenitis.

Precautions and Adverse Reactions: TYLENOL acetaminophen has rarely been found to produce any side effects. If a rare sensitivity reaction occurs, the drug should be stopped. It is usually well tolerated by aspirin-sensitive patients.

Usual Dosage: Doses may be repeated 4 or 5 times daily, but not to exceed 5 doses in 24 hours.
Children's TYLENOL Chewable Tablets: 1–2 years: one and one half tablets. 2–3 years: two tablets. 4–5 years: three tablets. 6–8 years: four tablets. 9–10 years: five tablets. 11–12 years: six tablets.
Children's TYLENOL Elixir: (special cup for measuring dosage is provided) 4–11 months: one-half teaspoon. 12–23 months: three-quarters teaspoon. 2–3 years: one teaspoon. 4–5 years: one and one-half teaspoons. 6–8 years: 2 teaspoons. 9–10 years: two and one-half teaspoons. 11–12 years: three teaspoons.
Infants' TYLENOL Drops: 0–3 months: 0.4 ml. 4–11 months: 0.8 ml. 12–23 months: 1.2 ml. 2–3 years: 1.6 ml. 4–5 years: 2.4 ml.
Note: Since Children's TYLENOL acetaminophen Chewable Tablets, Elixir and Drops are available without prescription as an analgesic, the following appears on the package labels: "WARNING: Consult your physician if fever persists for more than three days or if pain continues for more than five days. **Do not use if safety seals are broken. Keep this and all medication out of the reach of children. In case of accidental overdosage, contact a physician or poison control center immediately.**"

Overdosage: Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. In all cases of suspected overdose, immediately call your regional poison center or the Rocky Mountain Poison Center's toll-free number (800-525-6115) for assistance in diagnosis and for directions in the use of N-acetylcysteine as an antidote, a use currently restricted to investigational status. The occurence of acetaminophen overdose toxicity is uncommon in the pediatric age group. Even with large overdoses, children appear to be less vulnerable than adults to developing hepatotoxicity. This may be due to age-related differences that have been demonstrated in the metabolism of acetaminophen. Despite these differences, the measures outlined below should be immediately initiated in any child suspected of having ingested an overdose of acetaminophen.
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. If an acute dose of 150 mg/kg body weight or greated was ingested, or if the dose cannot be accurately determined, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours post-ingestion. If in the toxic range, liver function studies should be obtained and repeated at 24-hour intervals. The antidote N-acetylcysteine should be administered as early as possible, and within 16 hours of the overdose ingestion for optimal results. Following recovery there are no residual, structural or functional hepatic abnormalities.

How Supplied: Chewable Tablets (colored pink, scored, imprinted "TYLENOL")—Bottles of 30. Elixir (colored red)—bottles of 2 and 4 fl. oz. Drops (colored orange)—bottles of ½ oz. (15 ml.) with calibrated plastic dropper.
All packages listed above have child-resistant safety caps.

Shown in Product Identification Section, page 414

Junior Strength TYLENOL® acetaminophen Swallowable Tablets

Description: Each Junior Strength Swallowable Tablet contains 160mg acetaminophen in a small, coated, capsule shaped tablet.

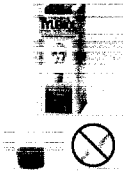
Actions: TYLENOL acetaminophen is an effective antipyretic/analgesic. It produces antipyresis through action on the hypothalmic heat-regulating center and

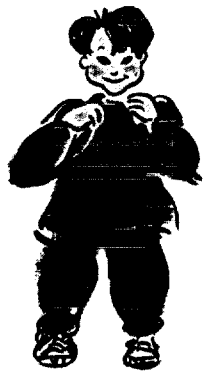
ATTACHMENT 2

PROFESSIONAL DOSING CHART

CHILDREN'S
TYLENOL®
acetaminophen

Dosing Chart

		Infants' Concentrated Drops 80 mg/0.8 mL	Children's Suspension Liquid and Elixir 160 mg/5 mL	Children's Chewable Tablets 80 mg each	Junior Strength Chewable Tablets/Caplets 160 mg each
		 YES NO	 YES NO		
	Dose ►	**dropperful**	**teaspoon**	**tablet**	**tablet/caplet**
Weight	**Age**				
6-11 lbs	0-3 mos	1/2			
12-17 lbs	4-11 mos	1	1/2		
18-23 lbs	12-23 mos	1-1/2	3/4		
24-35 lbs	2-3 yrs	2	1	2	
36-47 lbs	4-5 yrs		1-1/2	3	
48-59 lbs	6-8 yrs		2	4	2
60-71 lbs	9-10 yrs		2-1/2	5	2-1/2
72-95 lbs	11 yrs		3	6	3
96 lbs & over	12 yrs				4



Use only as directed.
NOTE: If possible, use weight to dose; otherwise use age. To arrive at the correct dose, weigh your child before giving TYLENOL. All dosages may be repeated every 4 hours, but not more than 5 times daily. A health care professional should be consulted for dosing for children under the age of two years.
WARNINGS:
- Children's TYLENOL® should not be taken for pain for more than 5 days or for fever for more than 3 days unless directed by a physician. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, a physician should be consulted because these could be signs of a serious condition.
- **Do not exceed recommended dose.** Taking more than the recommended dose (overdose) may not provide more relief and could cause serious health problems. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician or poison control center immediately. Prompt medical attention is critical even if you do not notice any signs or symptoms.
- Do not use with any other product containing acetaminophen.
- Do not use adult Extra Strength TYLENOL® products for children under 12 years of age.

Tips on Giving Medicine Correctly

- Know your child's weight. Many children's medicines are dosed by weight or age. The dose will change as your child grows.
- Read the package instructions carefully. Not all medicines should be given at the same hourly intervals or in the same amount.
- Follow the package instructions and give the full amount that is labeled for your child.
- Always use the dropper, dosage cup, or other measuring device that comes with the medicine. Other items like kitchen teaspoons may not be accurate. Never use spoons, droppers or cups that come with other medicines.
- Don't give medicine to a baby who is lying down; this could cause choking.
- Write down the time and amount of each dose given.

McNEIL
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Pediatric Pharmacology 3:321–327 (1983)

Pediatric Dosing of Acetaminophen

Anthony R. Temple, MD

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Acetaminophen (paracetamol, APAP) is one of the safest and most widely used analgesic-antipyretics in children. When compared to other analgesic-antipyretics, acetaminophen has been shown in many clinical studies to have equivalent efficacy. Based on available clinical and pharmacokinetic data, acetaminophen should be dosed with single doses in the range of 10–15 mg/kg at 4-hour intervals. However, many dosing schedules recommend inadequate amounts of acetaminophen. Dosing schedules based on weight can be constructed that will accurately keep each dose within the recommended range. Dosing also can be adapted to an age-based schedule, which will provide consistent dosing from infancy to adolescence. The principles used to derive the age-based dosing schedule have potential application for use with other pharmacologic agents, particularly nonprescription drugs.

Key words: acetaminophen, pharmacokinetics, pharmacodynamics, age-based dosage schedules

INTRODUCTION

Acetaminophen (paracetamol, APAP) is one of the safest and most widely used analgesic-antipyretics in children. In numerous clinical studies, acetaminophen has been shown to have equivalent efficacy to other available analgesic-antipyretics [Colgan and Mintz, 1957; Eden and Kaufman, 1967; Tarlin and Landrigan, 1972; Steele et al, 1972; Hunter, 1973; Simila et al, 1975, 1977]. However, its efficacy depends on administration of adequate doses [Windorfer and Vogel, 1976; Peterson et al, 1978]. Based on available clinical and pharmacokinetic data, acetaminophen should be dosed with single doses in the range of 10–15 mg/kg at 4-hour intervals. Worldwide, a multiplicity of dosing schedules are in use, many of which do not provide doses within this range. The purpose of this paper is to present data to support

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a specific dosing schedule for acetaminophen based on a dosage range of 10–15 mg/kg body weight.

The most commonly used dosage recommendations for acetaminophen have been based on the age of the child [Flower et al, 1980; Ryan, 1980; AMA Division of Drugs, 1983; Shirkey, 1980]. However, dosages based on weight and body surface area also have been used [AMA Divsion of Drugs, 1983; Shirkey, 1980; Lovejoy and Done, 1980; Yaffe, 1980]. Many dosing schedules appear to be based on fractions of adult doses (½, ¼, etc), with age breaks that do not adequately take into consideration changes in body mass of the growing child. Dosage based on weight and/or body surface area are a more accurate basis for calculating the optimal drug dosage for individual children [Zenk, 1979; Rane and Wilson, 1976]. However, body surface-area calculations are impractical for drugs made available without prescription, where dosage recommendations are placed on package labels and administered by nonhealth professionals, and are often awkward for clinicians as well. Thus for drugs like acetaminophen, dosing based on weight is preferable.

CLINICAL STUDIES

In determining appropriate dosing of drugs, pharmacodynamic measurements are important. Ideally, doses should be based on measurements of efficacy, related pharmacokinetic parameters, and other relevant dosage correlations. Pharmacodynamic and antipyretic efficacy studies of acetaminophen suggest that doses exceeding 10 mg/kg (and within the range of 10–15 mg/kg) are necessary for optimal antipyretic efficacy when given at 4-hour intervals. Several investigators have compared the antipyretic efficacy of doses of acetaminophen from 5 to 20 mg/kg. Table I summarizes five such studies, which demonstrate increasing maximum temperature decrement with increasing doses [Simila et al, 1975; Windorfer and Vogel, 1976; Peterson et al, 1978; Kienan et al, 1977]. Peak acetaminophen activity occurs between 1 and 2 hours with 5 mg/kg, around 3 hours with 10 mg/kg, and at 4 hours with 20 mg/kg.

Using composite data from these studies, a dose-response curve comparing the maximum observed temperature decrement (ΔT_{max}) at each of three doses as well as the duration of a significant temperature decrement can be constructed. With 5 mg/kg an average maximum decline of only 0.4°C occurs. With doses of 10 mg/kg an average maximum decline of 1.6°C occurs, and with doses of 20 mg/kg an average maximum decline of 2.0°C occurs. Not only does the maximum temperature decrement increase with increasing doses of acetaminophen, but the duration of antipyretic effect increases with increasing dose. An analysis of the duration of observed temperature decrement in excess of 1°C (ΔT_{opt}) shows that a dose of 5 mg/kg does not produce a satisfactory response at all, 10 mg/kg produces a 1°C or better response for up to 4 hours, and a 20 mg/kg dose produces a 1°C or better response for up to 7 hours. Thus, the data from these studies indicate that in order to produce satisfactory temperature reduction for at least 4 hours, a minimum single dose of 10 mg/kg is necessary.

Studies with pharmacokinetic measurements show a relationship between plasma level and antipyretic efficacy, with satisfactory antipyretic effect associated with plasma levels in a specific therapeutic range. A study conducted by Peterson et al [1978] compared doses of 10, 20, and 30 mg/kg with regard to antipyretic effect and plasma acetaminophen level. Peak plasma levels were 8.0 μg/ml for 10 mg/kg, 18.6

TABLE I. Comparison of Antipyretic Effect of Various Acetaminophen Doses

Dose (mg/kg)	Initial temperature (°C)	Mean temperature decrement (°C) (Hours following administration) 0.5	1.0	2.0	3.0	4.0	5.0	6.0	8.0	Maximum decrement (°C)
5[a]	39.5	0.3	0.4	0.4	0.3	0.3	0.1	—	0.1	0.4
10[b]	39.5	0.3	0.8	1.5	1.6	1.4	1.1	1.2	0.9	1.6
20[c]	39.6	0.4	1.4	1.9	—	2.0	—	—	1.9	2.0

[a]Windorfer and Vogel [1976].
[b]Simila et al [1975, 1979]; Windorfer and Vogel [1976]; Peterson et al [1978]; Kienanen et al [1977].
[c]Windorfer and Vogel [1976]; Peterson et al [1978].

μg/ml for 20 mg/kg, and 23.6 μg/ml for 30 mg/kg. A decline in temperature was noted within 30 minutes after drug administration with all three doses. Peak temperature decrement occurred at 2 hours with 10 mg/kg, between 2 and 4 hours with 20 mg/kg, and at 4 hours or later with 30 mg/kg. Peak temperature declines did not coincide with peak plasma levels, but inital rates and apparent duration of temperature reduction did correlate with dose and height of peak plasma level. Temperature reduction continued or was maintained as long as plama levels exceeded 5 μg/ml. Another study by Wilson et al [1982] has shown this same relationship between onset and maximum temperature reduction with plasma levels of acetaminophen, with regard both to peak levels and time to reach peak level. In this study doses averaging 9.9 mg/kg produced peak plasma levels of 9.3 μg/ml, with doses averaging 12.4 mg/kg producing peak levels of 14.6 μg/ml. Wilson et al [1982] also provides some useful pharmacokinetic modelling, which indicates that doses of 9.9 mg/kg given at 4-hour intervals could be expected to produce a plateau level within an appropriate therapeutic range after four to five doses. Additionally, giving a dose of 13.3 mg/kg at 4-hour intervals, with a nightly dose deleted each 24 hours, would maintain plasma levels within an appropriate therapeutic range even when given for several days.

A recent study by Powell and Nahata [1982] also evaluated at comparable pharmacodynamic relationships. Their study examined pharmacokinetic parameters and temperature reduction when doses of 12–15 mg/kg were given six times daily (every 4 hours) for 3 days or when doses of 24–30 mg/kg were given, three times daily (every 8 hours) for 3 days. Results of peak and trough levels of first and last doses of either 12–15 mg/kg given at 4-hour intervals, six times daily for 3 days, or 24–30 mg/kg given at 8-hour intervals, three times daily for 3 days show that plasma levels remain within an appropriate therapeutic range with this dosing schedule and confirmed that repetitive dosing in this manner does not result in accumulation to toxic levels. Taken altogether, the available data clearly indicate that doses of 10–15 mg/kg should be considered the optimum dose of acetaminophen for children when given at 4-hour intervals.

APPLICATIONS TO A DOSING SCHEDULE

As a practical matter, the concept of dosing acetaminophen within this range must be applied to available products in a way that will produce a satisfactory weight-

based dosing schedule and perhaps even a more reasonable approach to dosing by age. For these dosing schedules, a dosage unit of 80 mg was used, in order to coincide with the US FDA Monographs [1977] on analgesic-antipyretic agents and with the chewable acetaminophen tablet sizes available in the United States. Using doses that are increments of this dosage unit, compared to various weights and the resultant mg/kg doses, a schedule based on weight was constructed (Table II). This schedule provides gradual dosing increments of 40 or 80 mg as the child increases in weight. A graphic comparison of these weight-related doses to the optimal dosage range demonstrates that by using this weight-based schedule, virtually all dosing can be maintained within the 10–15 mg/kg range (Fig. 1). Using such a schedule allows for greater accuracy in dosing and greater consistency of response. When this dosage schedule is compared to doses based on body surface area, a reasonable fit occurs (Fig. 2), although these doses tend to produce a lower mg/m^2 doses at the lower end of the weight range (for 5–15 kg, range = 150–300 mg/m^2) compared to the mg/m^2 doses at higher weights (for 30–40 kg, range = 350–450 mg/m^2).

This dosing concept also can be applied to an age-related dosing schedule. Using age breaks that are consistent with the weight schedule an age-based schedule can be developed (Table III). This schedule is basically the same as that published in

TABLE II. Acetaminophen Dosing Recommendations Based on 10–15 mg/kg per Dose

Weight based schedule 80 mg unit		
	Weight	
Dose (mg)	(lbs)	(kg)
40	6–11	2.5– 5.4
80	12–17	5.5– 7.9
120	18–23	8.0–10.9
160	24–35	11.0–15.9
240	36–47	16.0–21.9
320	48–59	22.0–26.9
400	60–71	27.0–31.9
480	72–95	32.0–43.9
640	96 and over	44.0 and over

TABLE III. Acetaminophen Dosing Recommendations Based on 10–15 mg/kg per Dose

Age based schedule 80 mg unit	
Dose (mg)	Age
40	Under 4 months
80	4–11 months
120	12–23 months
160	2– 3 years
240	4– 5 years
320	6– 8 years
400	9–10 years
480	11–12 years
640	Over 12 years

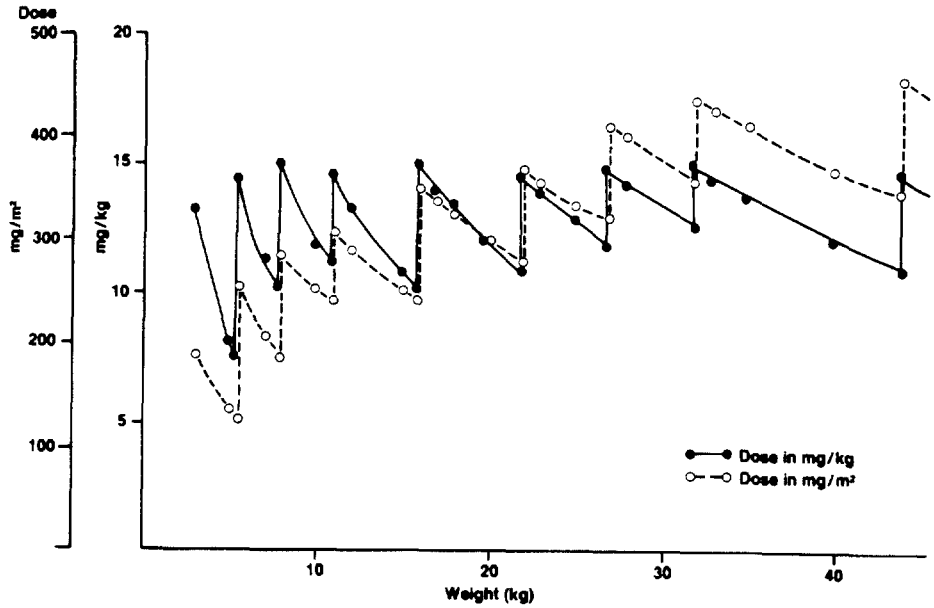

Figure 1. Comparison between dose in mg/kg and dose in mg/m^2 (B.S.A.) when doses are determined to approximate 10–15 mg/kg.

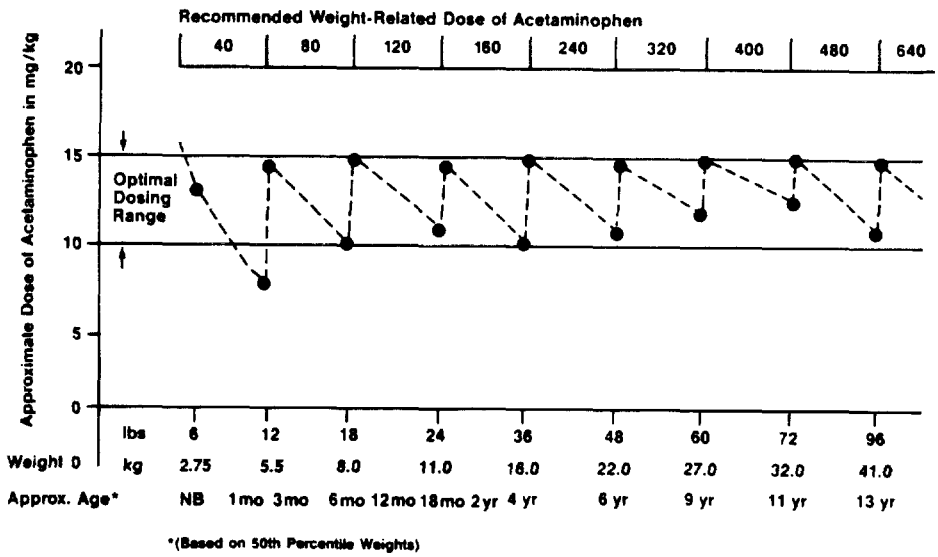

Figure 2. Comparison of weight-related doses (lbs. and kg) to recommended dosage increments and optimal dosage range of 10–15 mg/kg.

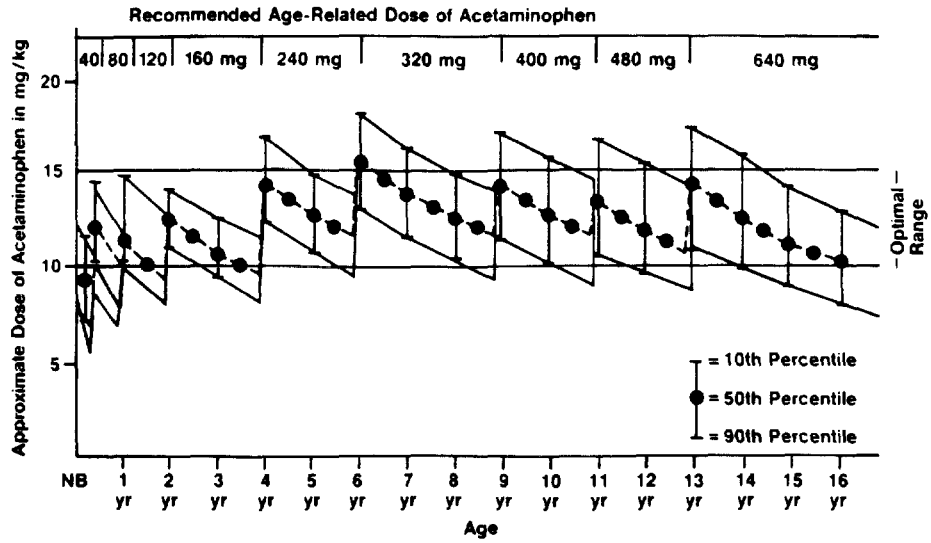

Figure 3. Comparison of recommended age-related doses of acetaminophen to optimal dosage range of 10–15 mg/kg for children at 10th, 50th and 90th percentiles.

the US FDA Proposed Monograph [1977] for children aged 2 and over, but also includes doses for children under age 2 and suggests that the same dose be used for children aged 11 and 12. When compared to previously used dosing schedules, it has the advantage of having 40 or 80 mg incremental steps with changes occurring every few months or years. A graphic representation of the recommended age-related doses, converted to approximate doses in mg/kg, in comparison to a dosage range of 10–15 mg/kg shows that for average weight children the age based dosing schedule quite adequately maintains the dose in the desired range (Fig. 3). For children under 1 year, the dose is somewhat lower. For very large (90th percentile or greater) children, there is tendency to underdose when dosing by age, which may result in diminished efficacy. For very small (10th percentile or smaller) children, there is a tendency to exceed the recommended dosage range. Thus, for children who are either relatively large or very small for their age, the clinician may prefer the weight-related schedule.

SUMMARY

In summary, pediatric dosing of acetaminophen should be based on doses in the range of 10–15 mg/kg. Pharmacodynamic assessments show that optimal temperature reduction may not occur with acetaminophen with doses less than 10 mg/kg. Pharmacokinetic assessments support dosing in the 10–15 mg/kg range both in terms of single acute doses as well as repetitive doses for up to 2 or 3 days. A dosing schedule has been constructed based on weight that will accurately keep each dose within the

recommended range. Dosing also can be adapted to an age-related schedule which will provide, for the average weight child, consistent dosing from infancy to adolescence.

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Pediatric Pharmacology 4:253–254 (1984)

Letter to the Editor:
Pediatric Dosing of Acetaminophen

The recent article by Temple concisely summarized research on acetaminophen dosage in pediatric patients and clarified current recommendations (Temple, 1984). We have expanded this information in chart form to simplify acetaminophen and aspirin antipyretic therapy in children (Table 1, p. 254). The chart has been readily accepted and utilized by parents, nurses, residents, and faculty physicians at our institution.

Although acetaminophen may be the preferred antipyretic agent due to its wide margin of safety and lack of side effects (Temple, 1983), both medications are equally effective in treating an uncomfortable child with a fever greater than 102°F (Yaffe, 1981; Schmitt, 1980). Done's (1979) guidelines for aspirin dosage have been adopted and extended to patients less than two years of age. Only the most common preparations, including adult 325 mg. tablets and interchanging children's chewable 80 mg. acetaminophen and 81 mg. (1¼ grain) aspirin tablets, have been listed. Weight limits are recorded in both pounds and kilograms. Doses of acetaminophen drops and elixir are prescribed in dropper or teaspoon amounts as well as milliliters. Instructions for computing dosage and verifying drug concentrations are provided.

Schechter's (1980) formula for calculating antipyretic dose based on the age of the patient (number of 81 mg. aspirin or 80 mg. acetaminophen tablets = [½ × age] + 1) corresponds closely to the table recommendations. Beginning at age one year and continuing to a maximum of eight tablets at age twelve, the child within the weight estimations will receive a dose ranging from 11.0 to 16.5 mg./kg. with a mean of 14.3 mg./kg. If half tablets are eliminated to simplify administration (eg, 3 rather than 3½ tablets for a five-year-old), the dose will range from 7.3 to 15.2 mg. with a mean of 13.0 mg./kg.

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TABLE I. Acetaminophen/Aspirin Antipyretic Dose by Age and Representative Weight—Actual Weights Should Be Used to Compute Dosage for Children Outside the Listed Weight Limits for Age (10–15mg/kg)

Age Group		0–3m	4–11m	12–23m	2–3y	4–5y	6–8y	9–10y	11y	≥ 12y
Weight (lbs)		6–11	12–17	18–23	24–35	36–47	48–59	60–71	72–95	≥ 96
(kgs)		2.5–5.4	5.5–7.9	8.0–10.9	11.0–15.9	16.0–21.9	22.0–26.9	27.0–31.9	32.0–43.9	≥ 44.0
Dose (mg)		40	80	120	160	240	320	400	480	640
*Preparation	Concentration									
Acetaminophen drops	80 mg/0.8 ml dropper	0.4 ml (½ drp)	0.8 (1)	1.2 (1½)	1.6 (2)	—	—	—	—	—
Acetaminophen elixir or syrup	160 mg/5 ml teaspoon	—	2.5 ml (½ tsp)	3.75 (¾)	5 (1)	7.5 (1½)	10 (2)	12.5 (2½)	15 (3)	—
Acetaminophen or Aspirin (children's chewable) tablets	80–81 mg tablet	—	1 tab	1½	2	3	4	5	6	8
Acetaminophen or aspirin (adult) tablets	325 mg/tablet	—	—	—	—	—	1 tab	1	1½	2

*CAUTION: The concentration and correct dose of specific brands should be verified prior to administration.

Underdosing of Acetaminophen by Parents

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ABSTRACT. The parents of 96 young children seen in an inner-city walk-in clinic for perceived or measured "fever" were asked about their management of the symptom. Eighty-eight (92%) administered acetaminophen, and of these, 67% gave less than the usual recommended dose of 10 to 15 mg/kg per dose. Underdosing was most commonly noted in the younger, lighter patient population. Of the parents who gave an acetaminophen elixer preparation (160 mg/5 mL), 26% measured the dose with the 0.8-mL dropper intended for use with the infant drops preparation (80 mg/0.8 mL), resulting in significant underdosing of acetaminophen (2.3 ± 1.3 mg/kg per dose). Health care professionals should specifically inquire about the details of acetaminophen administration when discussing antipyresis with parents. *Pediatrics* 1987; 80:630–633; *acetaminophen, fever.*

Acetaminophen is widely used for antipyresis in pediatric practice. Following the report of the Committee on Infectious Diseases of the American Academy of Pediatrics[1] associating salicylates with Reye syndrome, pediatricians have been increasingly recommending that acetaminophen be used for fever. It is also the preferred antipyretic in children because of its few side effects and low toxicity when compared with salicylates.[2,3] The primary concern regarding acetaminophen has been possible toxic overdose.[4–6] In our experience, underdosing of acetaminophen by parents is a more common phenomenon than overdosing. Although less serious in terms of morbidity, this practice may lead to ineffective treatment of fever and unnecessary visits to the emergency department or physician's office. It has been shown that reduction of fever is directly related to the dose of acetaminophen, with the optimal dose being 10 to 15 mg/kg per dose.[7] Giving less than the 10 mg/kg per dose results in minimal to no reduction of fever. Our objectives were to determine the frequency with which parents administered acetaminophen incorrectly when treating perceived fever in their children and to determine which factors predict incorrect dosing. Our hypothesis was that most parents giving an incorrect dose of acetaminophen give less than the minimal recommendation of 10 mg/kg per dose.

Received for publication Sept 8, 1986; accepted Jan 6, 1987
Reprint requests to (S.C.) 818 Pine St, Philadelphia, PA 19107.

METHODS

The study was conducted in the emergency department of The Children's Hospital of Philadelphia during a five-day period (March 10 to 14, 1986) from 9 AM to 6 PM. Parents were eligible if their child was less than or equal to five years of age and one of the parental complaints was a perceived or measured fever. They were interviewed by one of the investigators prior to the medical visit to ascertain how the parent treated fever and, if fever was treated, whether an antipyretic was used. If no antipyretic medication had been given, or if a non-acetaminophen preparation was used, the parent and child were excluded from analysis. Parents of children who gave acetaminophen (Tylenol, Tempra, Panadol) were asked what form and dose of the medicine had been used. To aid their recall,[7a] they were shown the infant drops (80 mg/0.8 mL), the children's elixir (160 mg/5 mL), and the children's chewable tablet (80 mg per tablet), as well as the infant dropper (0.8 mL), the standard 15-mL (3-teaspoon) elixir measuring cup, a 3-mL and 5-mL syringe, and a teaspoon. The parents were asked when and from where the dosage information was obtained, how often the medicine was administered, and whether they generally consulted a physician prior to giving the antipyretic.

Sociodemographic data were collected, including race, parental age, educational level (last grade completed), rank order in family, and method of reimbursement for the medical visit. Each child's age in months and weight in kilograms was recorded. Following completion of the study a milli-

gram per kilogram per dose of acetaminophen was calculated for each child, based upon parental information. Doses less than 10 mg/kg were considered inappropriately low, and those greater than 15 mg/kg were considered inappropriately high.

STATISTICAL ANALYSIS

Linear regression and Pearsons correlation were used to evaluate the relationship between two continuous variables. Differences among means were evaluated with analysis of variance or with the Kruskal-Wallis statistic when unequal variances were found. When significance among the means was found, sequential Mann-Whitney *U* tests were performed to determine where the differences occurred.

RESULTS

There were 97 parents eligible for enrollment. One parent declined to participate, and eight were excluded (three gave salicylates and five gave no antipyretics). Most of the parents were black, and the majority received medical assistance. The individual accompanying the child was usually the mother (95%), and the caretaker had completed high school 60% of the time. Of children seen, 39% were the eldest in their families, and 49% had one or two older siblings. The children had a mean age of 22.7 ± 15.6 months and a mean weight of 12.1 ± 3.8 kg.

Most of the parents gave medicine for a fever, and almost all who used a drug used an acetaminophen preparation (Table 1). With all forms of acetaminophen, 68% of the parents administered a dose less than the recommended 10 to 15 mg/kg per dose, with 31% of parents giving less than 6 mg/kg per dose. A dose greater than 15 mg/kg per dose was given 6% of the time (Figure).

There was no linear relationship found between dose of acetaminophen and age, weight, or number of children in the family. However, a parabolic relationship was noted between dose and age and weight; at young ages and low weights high and low doses were given. To evaluate this relationship, we categorized the dose variable as low dose (<10 mg/kg per dose), appropriate dose (10 to 15 mg/kg per dose), and high dose (>15 mg/kg per dose). Differences in the mean age and weight were found among these categories (Table 2). The mean age of the children was less in the underdosed group ($P < .0002$)[1] and in the overdosed group ($P < .002$) than in the appropriate dose group. The mean weight was also lower in the underdosed ($P < .0034$)[1] and overdosed ($P < .038$)[1] groups when compared with the appropriate dose group. Because of the high correlation between age and weight (.82), the independent effect of these variables could not be evaluated.

There was a difference in mean dose of acetaminophen among the methods used to measure the dose. The mean dose given with the infant dropper was lower (6.4 mg/kg per dose, $P < .0002$) than the mean doses given with other measuring devices. Of parents who gave the elixir, 26% gave it with the infant dropper. There were no differences found in

TABLE 1. Treatment Questionnaire

Question and Response	No. (%) of Parental Responses
What do you use to treat fever?* (n = 96)	
Nothing	1 (1)
Medicine	80 (83)
Medicine and cool bath	11 (12)
Bath alone	4 (4)
If medicine, what do you use?* (n = 91)	
Tylenol	83 (92)
Tempra	3 (3)
Panadol	2 (2)
Aspirin	3 (3)
What form of medicine (acetaminophen) do you use† (n = 88)	
Drops	45 (52)
Elixir	39 (44)‡
Chewable	4 (5)
If liquid (acetaminophen) preparation, what do you use to measure?† (n = 88)	
Infant dropper	55 (62)
Teaspoon	11 (13)
Measuring cup	16 (18)
Other	6 (7)
Where did you get dose information?† (n = 88)	
Physician	54 (61)
Nurse	1 (1)
Family/self	1 (1)
Bottle	27 (31)
Other	5 (6)
When did you last receive instructions?† (n = 88)	
<2 wk	29 (33)
2–8 wk	34 (39)
>8 wk	25 (28)
Do you call a physician prior to treating fever?† (n = 88)	
Yes	9 (10)
No	79 (90)

* Asked of all parents screened for study.
† Asked only of parents enrolled in study.
‡ Of those using elixir, 26.3% report using the 0.8-mL infant dropper to measure the dose.

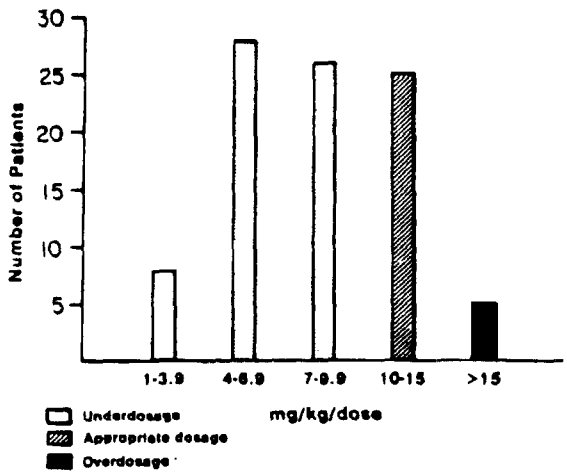

Figure. Number of children receiving acetaminophen.

TABLE 2. Relationship Between Acetaminophen Dose and Age and Weight*

Dose	No.	Age (mo)	Wt (kg)
Underdose	59	18.8 ± 14.2	11.5 ± 3.9
Appropriate dose	24	33.8 ± 15.6	14.0 ± 3.35
Overdose	5	16.6 ± 6.8	11.2 ± 1.69

* Results are means ± SD. Relationship with age determined by Kruskal-Wallis test: $\chi^2 = 14.11$, $P < .0009$; relationship with weight: $\chi^2 = 9.33$, $P < .009$.

dose among the other variables, including source of dosing information, timing of information, and whether or not the physician was called.

DISCUSSION

Fever is a common complaint in pediatrics.[8] Parents' misconceptions about fever abound and are the subjects of previous studies.[9-11] Kramer et al[9] found that many parents consider temperatures less than 38.0°C to be "fever" and treat accordingly. The rationale for treating fever has been debated, but most agree that the principal reason is to relieve discomfort.[2] We were concerned with parental perception of fever in the child and subsequent management of fever. Our findings are that underdosing of acetaminophen is the rule rather than the exception. The few who administered doses greater than the maximum recommended 15 mg/kg per dose correspond to the figure of 4% quoted elsewhere.[10]

The use of inappropriate dosing of acetaminophen was significantly related to age and weight of the child, with lower weight and younger age predictive of underdosing and overdosing. The majority of parents related that they had received instructions regarding acetaminophen dosing from a physician within the preceding 2 months, suggesting that physician may be advising a low dose. If the parents were inaccurate in their recollection and had actually received these instructions more than 2 months earlier, this would also be consistent with our findings, because the rapidly growing infant and toddler will quickly outgrow his or her last assigned acetaminophen dose. To help assure correct treatment, the prescriber should routinely calculate the acetaminophen dose for a small child on the basis of 15 mg/kg per dose rather than 10 mg/kg per dose. The bottles of acetaminophen should also be labeled with dose information for infants based on weight. The dosage schedule recommended by Temple[7] would provide parents with immediate information on dosing for infants older than 3 months of age.

The lack of a relationship between underdosing with acetaminophen and parental age, education, and number of preceding children has been demonstrated in previous studies of other aspects of parental knowledge about fever and its management.[9,11]

An additional finding of concern was the frequent use of the 0.8-mL infant dropper for administration of the children's elixir. Of parents who used acetaminophen elixir, 26% followed this practice, leading to marked underdosing of the drug (mean 2.3 + 1.3 mg/kg per dose). This practice was alluded to by Sweet,[12] but has not been quantified. Apparently, many parents purchase the less concentrated elixir as a refill for the smaller container of the more concentrated acetaminophen drops, and they continue to use the convenient infant dropper and to equate the dropper (0.8 mL) to the more familiar "teaspoon" (5 mL).[12]

Although our findings were based on a study of an inner city, lower socioeconomic population, and cannot be generalized, other parental misconceptions about fever have been found to transcend socioeconomic bounds.[11] The results underscore the need for the health care professional to inquire specifically about the details of administration of acetaminophen or of other medications available across the counter in forms with differing concentrations. Physicians must also be aware of the parental predilection to use the 0.8-mL infant dropper for the less concentrated elixir preparation. Identification of improper acetaminophen administration with appropriate physician intervention may prevent unnecessary medical visits for fever.

ACKNOWLEDGMENTS

This work was funded, in part, by the Robert Wood Johnson Foundation.

We thank Jessica Seidl-Friedman for her help as research assistant.

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OTC Cold Preparations, Pediatric *on page 753-756*

Overdose and Toxicology Information *on page 839-842*

Brand Names Acephen® [OTC]; Aceta® [OTC]; Apacet® [OTC]; Banesin® [OTC]; Dapa® [OTC]; Dorcol® [OTC]; Feverall™ [OTC]; Genapap® [OTC]; Junior Strength Panadol® [OTC]; Liquiprin® Infant Drops [OTC]; Meda-Cap® [OTC]; Myapap® Drops [OTC]; Neopap® [OTC]; Panadol® [OTC]; Redutemp® [OTC]; Ridenol® [OTC]; Snaplets-FR® Granules [OTC]; Tempra® [OTC]; Tylenol® [OTC]; Ty-Pap [OTC]; Uni-Ace® [OTC]

Synonyms APAP; N-Acetyl-P-Aminophenol; Paracetamol

Therapeutic Category Analgesic, Non-Narcotic; Antipyretic

Use Treatment of mild to moderate pain and fever; does not have antirheumatic or systemic anti-inflammatory effects

Pregnancy Risk Factor B

Contraindications Hypersensitivity to acetaminophen

Warnings May cause severe hepatic toxicity with overdose

Precautions Some products (eg, Children's Tylenol® chewable tablets) contain aspartame; aspartame is metabolized to phenylalanine and must be avoided or used with caution in patients with phenylketonuria

G-6-PD deficiency: Although several case reports of acetaminophen-associated hemolytic anemia have been reported in patients with G-6-PD deficiency, a direct cause and effect relationship has not been well established (concurrent illnesses such as fever or infection may precipitate hemolytic anemia in patients with G-6-PD deficiency); therefore, acetaminophen is generally thought to be safe when given in therapeutic doses to patients with G-6-PD deficiency.

Adverse Reactions

Dermatologic: Rash

Hematologic: Blood dyscrasias (neutropenia, pancytopenia, leukopenia)

Hepatic: Hepatic necrosis with overdose

Renal: Renal injury with chronic use

Miscellaneous: Hypersensitivity reactions (rare)

Drug Interactions Enzyme inducers (barbiturates, carbamazepine, phenytoin) and alcohol (especially chronic use) can increase hepatotoxicity; rifampin may decrease acetaminophen's therapeutic effect

Food Interactions Rate of absorption may be decreased when given with food high in carbohydrates

Mechanism of Action Inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Pharmacokinetics

Protein binding: 20% to 50%

Metabolism: At normal therapeutic dosages the parent compound is metabolized in the liver to sulfate and glucuronide metabolites, while a small amount is metabolized by microsomal mixed function oxidases to a highly reactive intermediate (N-acetyl-imidoquinone) which is conjugated with glutathione and inactivated; at toxic doses (as little as 4 g in a single day) glutathione can become depleted, and conjugation becomes insufficient to meet the metabolic demand causing an increase in N-acetyl-imidoquinone concentration, which is thought to cause hepatic cell necrosis.

Half-life:

Neonates: 2-5 hours

Adults: 1-3 hours

Time to peak serum concentrations: 10-60 minutes after normal oral doses, but may be delayed in acute overdoses

Usual Dosage Oral, rectal:

Neonates: 10-15 mg/kg/dose every 6-8 hours as needed

Infants and Children: 10-15 mg/kg/dose every 4-6 hours as needed; do **not** ex-

Acetaminophen

Age	Dosage (mg)	Age	Dosage (mg)
0-3 mo	40	4-5 y	240
4-11 mo	80	6-8 y	320
1-2 y	120	9-10 y	400
2-3 y	160	11 y	480

ceed 5 doses in 24 hours; alternatively, the following doses may be used. See table.

Children ≥12 years and Adults: 325-650 mg every 4-6 hours or 1000 mg 3-4 times/day; do **not** exceed 4 g/day

Administration Oral: Administer with food to decrease GI upset

Reference Range Toxic concentration with probable hepatotoxicity: >200 µg/mL at 4 hours or 50 µg/mL at 12 hours after ingestion of overdose

Patient Information Avoid alcohol; do not take longer than 10 days without physician's advice

Additional Information Some elixir preparations contain sodium benzoate; drops contain saccharin

Dosage Forms

Caplet: 160 mg, 325 mg, 500 mg

Capsule: 325 mg, 500 mg

Drops: 100 mg/mL (15 mL); 120 mg/2.5 mL (35 mL)

Granules, premeasured packs: 80 mg (32s)

Elixir: 80 mg/5 mL (120 mL); 120 mg/5 mL (5 mL, 10 mL, 13.5 mL, 25 mL, 27 mL, 120 mL, 480 mL, 3780 mL); 130 mg/5 mL (12.5 mL, 25 mL); 160 mg/5 mL (5 mL, 10 mL, 20 mL, 120 mL, 240 mL, 500 mL, 3780 mL); 325 mg/5 mL (480 mL, 3780 mL)

Liquid, oral: 160 mg/5 mL (2.5 mL, 5 mL, 60 mL, 120 mL, 240 mL, 480 mL); 500 mg/15 mL (240 mL)

Powder, in capsules: 80 mg, 160 mg

Suppository, rectal: 80 mg, 120 mg, 125 mg, 300 mg, 325 mg, 650 mg

Suspension, oral: 48 mg/mL, 100 mg/mL, 160 mg/5 mL

Tablet: 120 mg, 325 mg, 500 mg, 650 mg

Tablet, chewable: 80 mg, 120 mg, 160 mg

Acetaminophen and Codeine Phosphate

(a seet a min' oh fen & koe' deen fos' fate)

Related Information

Overdose and Toxicology Information *on page 839-842*

Brand Names Capital® and Codeine; CodAphen®; Margesic® No. 3; Tylenol® With Codeine

Synonyms Codeine Phosphate and Acetaminophen

Therapeutic Category Analgesic, Narcotic

Use Relief of mild to moderate pain

Restrictions C-III, C-V

Pregnancy Risk Factor C

Contraindications Hypersensitivity to acetaminophen or codeine phosphate

Warnings Tablets contain metabisulfite which may cause allergic reactions

Precautions Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (morphine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone) or respiratory disease/compromise

Adverse Reactions

Cardiovascular: Palpitations, hypotension, bradycardia, peripheral vasodilation

Central nervous system: CNS depression, dizziness, drowsiness, sedation, increased intracranial pressure

Dermatologic: Pruritus

Endocrine & metabolic: Antidiuretic hormone release

Gastrointestinal: Nausea, vomiting, constipation, biliary tract spasm

Genitourinary: Urinary retention

Ocular: Miosis

Respiratory: Respiratory depression

Miscellaneous: Histamine release, physical and psychological dependence with prolonged use

(Continued)

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Pediatric Diagnosis & Treatment

Eleventh Edition

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have not been reported for therapeutic agents. Quantitative drug overdose of the infant via breast milk is virtually never a problem.

Before administering a drug to a lactating woman, the following questions should be answered:

(1) Is the maternal drug therapy really necessary?

(2) Is this the least toxic drug that is effective?

(3) Can the dosing schedule be arranged to minimize delivery of the drug to the infant?

(4) Would this drug be given directly to the infant if the infant had an appropriate pediatric illness?

(5) In those instances where parenteral medications are given to the mother, is the drug absorbed by the oral route as it is delivered to the infant?

(6) Are idiosyncratic or allergic reactions a particular concern for this infant?

(7) Are there side effects? Will they be easily recognized (eg, drowsiness, rash, etc)?

(8) Does the infant have a known medical problem (eg, hepatic disease or renal disease) that would diminish the drug's excretion and thereby allow it to accumulate in the infant?

(9) Does the infant have a suspected medical problem (eg, suspected infection masked by low-dose antibiotic delivery via milk) whose eventual diagnosis might be delayed by subtherapeutic doses of the maternal drug?

(10) Will the amount of drug delivered via breast milk come close to approaching a therapeutic dose in the infant?

The answers to these questions usually will give the health care provider the information needed to know whether a drug should be given to the mother.

Quantitative drug overdose of the infant via breast milk is virtually never an issue, but idiosyncratic or allergic reactions to drugs are often not dose-related, and this aspect of drug administration should be kept in mind.

Some drugs are relatively safe in the adult (eg, radioactive iodine) but are associated with higher toxicity rates in children. These drugs, as well as other radiolabeled compounds, many cancer chemotherapeutic agents, and organ-selective toxic substances, should not be given to the mother if breast feeding is to be continued.

AVERAGE DRUG DOSAGES FOR CHILDREN*

Acetaminophen: Dose based on weight is 10–15 mg/kg orally. Dose based on age is generally as follows: 0–3 months, 40 mg; 4–11 months, 80 mg; 12–23 months, 120 mg; 2–3 years, 160 mg; 4–5 years, 180 mg; 6–8 years, 320 mg; 9–10 years, 400 mg; 11–12 years, 480 mg. May be repeated up to 5 times in 24 hours.

Acetazolamide: 5–30 mg/kg/d orally every 6–8 hours (Adult = 5 mg/kg/d.) For hydrocephalus, 20–55 mg/kg/d orally in two or three divided doses. For anticonvulsant use, see Table 22–15.

Acetylcysteine: For acetaminophen antidote, use 20% solution diluted 3:1 with juice, water, or carbonated beverage, 140 mg/kg orally (loading dose) followed by 17 doses of 70 mg/kg orally every 4 hours.

ACTH (adrenocorticotropic hormone, corticotropin): For infantile spasms, usually 20–40 units/d or (in gel form) 80 units every other day intramuscularly. For anticonvulsant use, see Seizure Disorders in Chapter 22.

Acyclovir: For herpes simplex infections and in neonates and children, 30 mg/kg/24 h intravenously every 8 hours for 10–14 days. For severe genital herpes, 15 mg/kg/24 h intravenously every 8 hours for 5 days.

Albumin, human 25%: 0.5–1 g/kg intravenously as 25 g/dL solution. Maximum, up to 25 g per dose, as required.

Albuterol: For children 2–6 years, 0.1 mg/kg orally to a maximum of 2 mg/dose three times daily. For children 6–12 years, 2 mg orally three or four times daily.

Alprostadil (prostaglandin E_1): To maintain patency of ductus arteriosus in patients with congenital heart lesions, 0.05–0.1 μg/kg/min by continuous infusion.

Aluminum hydroxide gel: 5–15 mL orally with meals.

Amantadine hydrochloride: 4.4–8.8 mg/kg/d orally.

Aminocaproic acid: 200 mg/kg orally, then 100 mg/kg/dose orally every 6 hours for 3–7 days (adult maximum = 30 g/24 h).

Aminophylline: Intravenously, 4–6 mg/kg every 6 hours or by continuous infusion of 0.9 mg/kg/h. High infusion rates may be necessary in children (see Special Considerations in Pediatric Drug Dosage, above). Intramuscular or rectal administration is not recommended.

Ammonium chloride: For urinary acidification, 75 mg/kg/d orally in four divided doses.

Apomorphine: Not indicated in pediatric practice.

Aspirin: Not recommended for routine analgesic or antipyretic use in children. For rheumatoid arthritis, 80–100 mg/kg/d to maintain a blood level of 20–30 mg/dL. (Adult maximum = 6–8 g/d.) Monitor plasma levels and liver function during therapy.

Atropine sulfate: 0.01–0.02 mg/kg subcutane-

*For drugs discussed in other chapters, consult the index.

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ACETAMINOPHEN (N-Acetyl-P-Aminophenol, APAP) (Cont.)

Administration and Dosage:

Oral: Adults - 325-650 mg every 4 to 6 hrs, or 1 g 3-4 times/day. Do not exceed 4 g/day.
Children - May repeat doses 4 or 5 times daily; do not exceed 5 doses in 24 hours.

Acetaminophen Dosage for Children

Age (years)	Dosage (mg)	Age (years)	Dosage (mg)
0-3 months	40	4-5	240
4-11 months	80	6-8	320
1-2	120	9-10	400
2-3	160	11	480

A 10 mg/kg/dose schedule has also been recommended.

Suppositories: Adults - 650 mg every 4 to 6 hrs. Give no more than 6 in 24 hours.
Children (6 to 12) - 325 mg every 4 to 6 hours. Give no more than 2.6 g in 24 hours.
Children (3 to 6) - 120 mg every 4 to 6 hours. Give no more than 720 mg in 24 hrs.
Children (< 3) - Consult physician.

Storage: Store suppositories below 27°C (80°F) or refrigerate.

				C.I.*
otc	**Acetaminophen** (Various, eg, Balan, Bioline, Dixon-Shane, Goldline, Harber, Major, Moore, Roxane, Rugby, Schein)	**Suppositories:** 120 mg	In 12s, 50s, 100s and UD 12s, 50s, 100s, 500s and 1000s.	401+
otc	**Acetaminophen Uniserts** (Upsher-Smith)		In UD 12s and 50s.	542
otc	**Acephen** (G & W Labs)		In 12s, 50s and 100s.	464
otc	**Feverall, Children's** (Upsher-Smith)		In 6s.	310
otc	**Suppap-120** (Raway)		In 12s, 50s, 100s, 500s, 1000s.	446
otc	**Neopap** (Alcon)	**Suppositories:** 125 mg	In 12s.	975
otc	**Acetaminophen** (Harber)	**Suppositories:** 300 mg	In 12s.	237
otc	**Acetaminophen** (Various, eg, Balan, Baxter, Rugby)	**Suppositories:** 325 mg	In 12s and 100s.	188+
otc	**Acetaminophen Uniserts** (Upsher-Smith)		In UD 12s and 50s.	219
otc	**Acephen** (G & W Labs)		In 12s, 50s and 100s.	175
otc	**Feverall, Junior Strength** (Upsher-Smith)		In 6s.	123
otc	**Suppap-325** (Raway)		In 100s.	100
otc	**Acetaminophen** (Various, eg, Balan, Bioline, Goldline, Harber, Lannett, Major, Roxane, Rugby, Schein, Vangard)	**Suppositories:** 650 mg	In 10s, 12s, 50s, 100s, 500s and UD 12s, 50s, 100s, 500s and 1000s.	82+
otc	**Acetaminophen Uniserts** (Upsher-Smith)		In 12s, 50s and 500s.	117
otc	**Acephen** (G & W Labs)		In 12s, 50s, 100s and 500s.	89
otc	**Suppap-650** (Raway)		In 50s, 100s, 500s and 1000s.	75
otc	**Acetaminophen** (Various, eg, Balan, Dixon-Shane, Gen-King, Major, Mason, Moore, Rugby, Schein)	**Tablets, chewable:** 80 mg	In 30s, 50s, 100s and 1000s.	81
otc	**Apacet** (Parmed)		In 100s.	30
otc	**Anacin-3, Children's** (Whitehall)		Scored. Cherry flavor. In 30s.	183
otc	**Genapap, Children's** (Goldline)		Pink. In 30s.	175
otc *sf*	**Panadol, Children's** (Glenbrook)		(#P). Scored. Fruit flavor. In 30s.	159

* Cost Index based on cost per 325 mg. # Product identification code. *sf* - Sugar free.

(Continued on following page)

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release tablets, but that an additional determination of plasma or serum acetaminophen concentrations from a sample obtained 4–6 hours after the initial sample also should be evaluated using the nomogram. In cases where it is unclear whether high doses of the drug were ingested as extended-release tablets or as conventional preparations of acetaminophen, the manufacturer suggests that overdosage of the drug be managed as if extended-release preparations were ingested.

In addition to plasma or serum acetaminophen concentrations, baseline prothrombin time, BUN, blood glucose concentration, and serum AST (SGOT), ALT (SGPT), bilirubin, creatinine, and electrolyte concentrations should be determined. Prothrombin time, blood glucose concentration, and serum AST, ALT, bilirubin, and electrolyte concentrations should be determined at 24-hour intervals for at least 96 hours after the time of ingestion; if toxicity is evident, these parameters should continue to be monitored at least daily as necessary. Fluid and electrolyte balance should be maintained; use of diuretics and forced diuresis should be avoided. Hypoglycemia should be treated as necessary. If the prothrombin time is greater than 1.5 times the control value, phytonadione should be administered; if the prothrombin time is greater than 3 times the control value, fresh frozen plasma should be given. If hepatic or renal impairment develops, appropriate laboratory parameters should be monitored until values return toward normal. A serum bilirubin concentration greater than 4 mg/dL and a prothrombin time greater than 2.2 times the control value may indicate impending hepatic encephalopathy. Hemodialysis or charcoal hemoperfusion may be useful in enhancing the elimination of acetaminophen from the body, but are generally *not* recommended. Peritoneal dialysis is ineffective.

Drug Interactions

Chronic ingestion of large doses of acetaminophen has been reported to slightly potentiate the effects of coumarin- and indandione-derivative anticoagulants but reports are conflicting. This effect appears to be of little, if any, clinical importance and acetaminophen is preferable to salicylates when a mild analgesic or antipyretic is required in patients receiving coumarin or indandione derivatives.

The possibility of severe hypothermia should be kept in mind in patients receiving concomitant phenothiazine and antipyretic therapy.

Since there is some evidence that chronic, excessive consumption of alcohol may increase the risk of acetaminophen-induced hepatotoxicity, chronic alcoholics should be cautioned to avoid regular or excessive use of acetaminophen, or alternatively, to avoid chronic ingestion of alcohol. At least one manufacturer states that patients who ingest 3 or more alcohol-containing drinks daily should consult their clinician before using acetaminophen.

Anticonvulsants (including phenytoin, barbiturates, carbamazepine) that induce hepatic microsomal enzymes may increase acetaminophen-induced liver toxicity because of increased conversion of the drug to hepatotoxic metabolites. In addition, concomitant administration of isoniazid with acetaminophen also may result in an increased risk of hepatotoxicity, but the exact mechanism of this interaction has not been established. The risk of acetaminophen-induced hepatic toxicity is substantially increased in patients ingesting larger than recommended dosages of acetaminophen while receiving anticonvulsants or isoniazid. Usually, no dosage reduction is required in patients receiving concomitant administration of therapeutic dosages of acetaminophen and anticonvulsants; however, patients should limit self-medication with acetaminophen while receiving anticonvulsants or isoniazid.

Laboratory Test Interferences

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Dosage and Administration

■ Administration

Acetaminophen usually is administered orally. In patients who cannot tolerate oral medication, acetaminophen may be administered rectally as suppositories; however, the rectal dose required to produce the same plasma concentrations may be higher than the oral dose. Acetaminophen preparations for self-medication should not be used unless seals on the tamper-resistant packaging are intact.

■ Dosage

Acetaminophen should not be used for *self-medication* of pain for longer than 10 days in adults or 5 days in children, unless directed by a physician, since pain of such intensity and duration may indicate a pathologic condition requiring medical evaluation and supervised treatment.

Acetaminophen should not be used in adults or children for *self-medication* of marked fever (greater than 39.5°C), fever persisting longer than 3 days, or recurrent fever, unless directed by a physician, since such fevers may indicate serious illness requiring prompt medical evaluation.

To minimize the risk of overdosage, no more than 5 doses of acetaminophen should be administered to children for analgesia or antipyresis in any 24-hour period, unless directed by a physician.

For analgesia or antipyresis in adults or children older than 11 years of age, the usual oral or rectal dosage of acetaminophen is 325–650 mg every 4–6 hours as necessary, but should not exceed 4 g daily; higher single doses (e.g., 1 g) may be useful for analgesia in some patients. For analgesia or antipyresis, children may receive the following *approximate* oral or rectal doses every 4–6 hours as necessary: children 11 years of age, 480 mg; children 9–10 years of age, 400 mg; children 6–8 years of age, 320 mg; children 4–5 years of age, 240 mg; and children 2–3 years of age, 160 mg. Children younger than 2 years of age may receive the following oral doses every 4–6 hours as necessary: children 1–2 years of age, 120 mg; children 4–11 months of age, 80 mg; and children up to 3 months of age, 40 mg. Rectal dosage in children younger than 2 years of age must be individualized. The usual oral dosage of acetaminophen (as 650-mg extended-release tablets) for analgesia in adults and children 12 years of age and older is 1.3 g every 8 hours as necessary, not to exceed 3.9 g daily. Extended-release acetaminophen tablets should not be crushed, chewed, or dissolved in a liquid.

Preparations

Acetaminophen

Powder*

Oral		
Capsules	500 mg*	
Capsules (containing a powder for solution)	80 mg	**Feverall® Sprinkle Caps® Children's**, Upsher Smith
	160 mg	**Feverall® Sprinkle Caps® Junior Strength**, Upsher Smith
For solution	1 g/packet	**Stanback® AF Extra-Strength Powder**, Stanback Company
Solution	120 mg/5 mL*	**Aceta®** (with alcohol 7%), Century
	130 mg/5 mL	**Acetaminophen Solution** (with alcohol 10%), UDL
	160 mg/5 mL*	**Genapap® Children's**, Goldline
		Panadol® Children's (with propylene glycol), SmithKline Beecham
		PediApap®, Central
		Tempra® 2 Toddler's Syrup, Mead Johnson
		Tylenol® Children's Elixir (with propylene glycol), McNeil
		Uni Ace® Children's, United Research
	48 mg/mL	**Liquiprin® Drops** (with parabens), Menley & James
	167 mg/5 mL	**Tylenol® Extra Strength** (with alcohol 7%), McNeil
	100 mg/mL*	**Genapap® Drops Infant's**, Goldline
		Panadol® Drops Children's (with parabens and propylene glycol), SmithKline Beecham
		Tempra® 1 Infant's Drops, Mead Johnson
		Tylenol® Drops Infant's (with butylparaben and propylene glycol), McNeil
		Uni Ace® Drops Infant, United Research
Suspension	160 mg/5 mL	**Tylenol® Suspension Children's** (with butylparaben and propylene glycol, cherry flavor), McNeil
	100 mg/mL	**Tylenol® Suspension Drops Infant's** (with butylparaben and propylene glycol; grape flavor), McNeil
Tablets	325 mg*	**Aceta®**, Century
		Genapap®, Goldline
		Genebs®, Goldline
		Panex®, Roberts

Rudolph's Pediatrics 19th edition

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APPENDIX C

Medication Table

Robert H. Levin and Karin E. Zenk

This table is largely a summary of the dosage recommendations in eight sources. Each of these books has specific references for the uses of each medication (see References). *Before any of these drugs is used, the package insert or other appropriate information should be consulted.*

Abbreviations of routes of administration: ET = into endotracheal tube; IC = intracardiac; IM = intramuscular; IT = intrathecal; IV = intravenous; PO = oral; PR = rectal; SC = subcutaneous; SL = sublingual. *Other abbreviations:* D5W = 5% dextrose solution in distilled water; NE = none established; NS = normal saline.

Note: Some drugs listed may be known by other names. See note at end of this appendix.

Medication	Route	Dose			Discussion
		Neonatal	*Pediatric*	*Adult*	
Acebutolol	PO	NE	NE	*Initial:* 400 mg once or twice daily; titrate dose to effect to 400–1200 mg/24 h given twice daily	Adjust dose for renal impairment; a β_1-selective β-adrenergic blocker
Acetaminophen	PO,PR	40 mg 4–5 times daily **Preterm:** *PO:* 10 mg/kg dose	Give doses 4–5 times daily, not to exceed 5 doses/d *Max:* 4 g/d **3–5 kg:** 40 mg/dose **6–8 kg:** 80 mg **9–10 kg:** 120 mg **11–16 kg:** 160 mg **17–21 kg:** 240 mg **22–27 kg:** 320 mg **28–32 kg:** 400 mg **33–43 kg:** 480 mg	325–650 mg q4–6h *Max:* 4 g/24 h	Has no anti-inflammatory effects; adjust dose for renal impairment; hepatic toxicity with serum levels >200 μg/mL
Acetazolamide	IV,IM,PO	5–55 mg/kg/24 h q6–12 h	5–55 mg/kg/24 h q6–12h	250 mg once daily or 500 to 1000 mg q6–12h	Once daily or every other day low doses for diuretic or urinary alkalinization, high doses for epilepsy or glaucoma, and highest dose for hydrocephalus; adjust for renal impairment. IV administration preferred due to pain with IM injection
Acetylcysteine	PO	NE	*Initial:* 140 mg/kg/dose, then every 4 h use 70 mg/kg/dose for a total of 17 doses	*Initial:* 140 mg/kg/dose, then q4h use 70 mg/kg/dose for a total of 17 doses	Use as antidote for acetaminophen overdose; use 20% solution and dilute to 5% with cola or other soft drinks; has best effects if used within 12 h of ingestion but can be used up to 24 h postingestion. This product is also used by inhalation to decrease the viscosity of pulmonary mucus secretions
Actinomycin D	IV	NE	15 μg/kg/24 h in 4–5 divided doses for 5 d or 2400 μg/m² total over 1 wk	0.5 mg daily for 5 d	Monitor blood count, cellulitis with extravasation; may need second course after 3 wk
Acyclovir	IV,PO	*IV:* 30 mg/kg/d given q8h as a 1-h infusion	<12 y: *IV:* 750 mg/m²/24 h given q8h as a 1-h infusion >12 y: *Initial: PO:* 200 mg given 5 times daily for 10 d *Chronic:* 200 mg 3–5 times daily for up to 6 mo *Intermittent:* 200 mg given 5 times a day for 5 d and restart at earliest sign of recurrence	*IV:* 15 mg/kg/24 h given q8h as 1 h infusion. *PO: Initial, chronic, and intermittent:* same as for > 12 y	This product is also available topically; IV dosing is for 7 d for mucosal or cutaneous involvement or for immunocompromised patients, and 5 d for initial severe genital herpes; adjust dose for renal impairment

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For WEEKEND Delivery check here (Extra Charge. Not available at all locations)

☐ Saturday Delivery (Available for FedEx Priority Overnight and FedEx 2Day only)
☐ NEW Sunday Delivery (Available for FedEx Priority Overnight only)

810440445600

4a Express Package Service *Packages under 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Priority Overnight (Next business morning)
XX FedEx Standard Overnight (Next business afternoon)
☐ FedEx First Overnight (Earliest next business morning delivery to select locations) **(Higher rates apply)**
☐ FedEx 2Day (Second business day)
☐ FedEx Express Saver (Third business day)
FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Overnight Freight (Next business day)
☐ FedEx 2Day Freight (Second business day)
☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging ☐ FedEx Letter XX FedEx Pak ☐ FedEx Box ☐ FedEx Tube ☐ Other Pkg.
Declared value limit $500

6 Special Handling (One box must be checked)

Does this shipment contain dangerous goods?* ☐ No ☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 ____ x ____ kg
☐ Cargo Aircraft Only

*Dangerous Goods cannot be shipped in FedEx packaging

7 Payment

Bill to: ☒ Sender (Account No. in Section 1 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check ☐ Obtain Recipient FedEx Account No.
(Enter FedEx Account No. or Credit Card No. below)

Total Packages	Total Weight	Total Declared Value	Total Charges
1	2	$ .00	$

* When declaring a value higher than $100 per shipment, you pay an additional charge. See **SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY** section for further information.

Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

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Questions?
Call 1·800·Go·FedEx® (800)463-3339

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WCSL 1298
Rev. Date 7/98
Part #153923ps
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PRINTED IN U.S.A.

98N-0044