ACQUIRE

Journal of Case Reports and Medical History

Open Access

Mini Review Article

Volume 1 – Issue 1

Clinical Pharmacology of Paracetamol in Infants and Children

Gian Maria Pacifici *

Associate Professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy

***Corresponding author:** Gian Maria Pacifici, via Sant'Andrea 32, 56127 Pisa, Italy

Received date: 16 September, 2021 | **Accepted date:** 1 October, 2021 | **Published date:** 6 October, 2021

Citation: Pacifici GM (2021) Clinical Pharmacology of paracetamol in Infants and Children. J Case Rep Med Hist 1(1). doi https://doi.org/10.54289/JCRMH2100102

Abstract

Paracetamol (acetaminophen) has analgesic and antipyretic effects similar to those of aspirin but has only weak anti-inflammatory effects. It is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. The major metabolites of paracetamol are paracetamol glucuronide and paracetamol sulphate and the minor metabolites are mercapturic acid cysteine conjugates and N-acetyl-p-benzoquinone imine. The last is a highly reactive intermediate and it reacts with sulfhydryl groups in glutathione and is harmless. Paracetamol may be administered orally, rectally, or intravenously. In infants, the oral dosing of paracetamol consist in a loading dose of 20 mg/kg following by subsequent doses of 10 to 15 mg/kg, and in children, the dose varies with the child age and body-weigh. Paracetamol has been found efficacy and safe in infants and children but it may induce adverse-effects. The elimination half-life of paracetamol is 11.0 and 4.38 hours in more immature preterm infants and in less immature preterm infants, respectively, and it is 3.45 hours in children. Propranolol interacts with drugs. The prophylaxis, treatment, and trials with paracetamol have been investigated in infants and children. Paracetamol may induce toxicity and it crosses the human placenta and migrates into the breast milk in significant amounts. The aim of this study in the review of paracetamol dosing, efficacy and safety, adverse-effects, metabolism, pharmacokinetics, drug interaction, prophylaxis, treatment, trials, toxicity in infants and children, and paracetamol transfer across the human placenta and migration into the breast milk.

Keywords: paracetamol; dosing; efficacy and safety; adverse effects; metabolism; pharmacokinetics; drug interaction; prophylaxis; treatment; trials; toxicity; placenta; breast milk; infants; children.

Abbreviations: COX: cyclooxygenase.

Introduction

General considerations

Acetaminophen (paracetamol; N-acetyl-p-aminophenol) is the active metabolite of phenacetin. Acetaminophen raises the threshold to painful stimuli, thus exerting an analgesic effect against pain due to a variety of aetiologies. Acetaminophen is available without a prescription and is used as a common household analgesic by children and adults. It also is available in fixed-dose combination containing narcotic and nonnarcotic analgesics (including aspirin and other salicylates), barbiturates, caffeine, vascular headache remedies, sleep aids, toothache remedies, antihistamines, antitussives, decongestants, expectorants, could and flu preparations, and some throat treatments. Acetaminophen is well tolerated; however, overdosage-two-thirds of which are

intentionally induced - can cause severe hepatic damage; it leads to nearly 80,000 emergency department visits and 30,000 hospitalizations annually in the U.S. The maximum FDA-recommended dose of acetaminophen is 4 grams daily **[1]**.

Mechanism of action of paracetamol

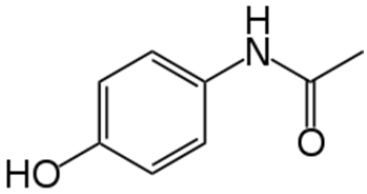
Paracetamol has analgesic and antipyretic effects similar to those of aspirin but has only weak anti-inflammatory effects. It is a nonselective cyclooxygenase (COX) inhibitor which acts at the peroxide site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. The presence of high concentrations of peroxides, as occur at sites of inflammation, reduces COX-inhibitory activity **[1]**.

Absorption, distribution, metabolism and elimination of paracetamol

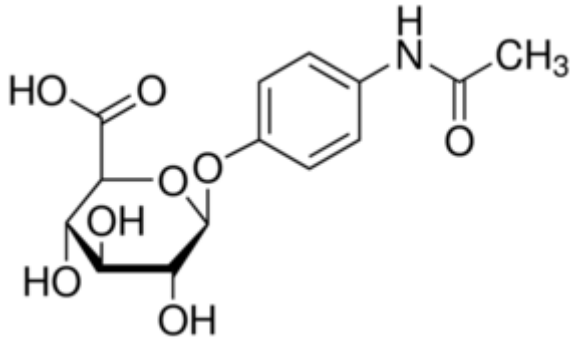
Oral paracetamol has excellent bioavailability. Peak plasma concentrations occur within 30 to 60 min, and in adult the elimination half-life is about 2 hours. Paracetamol is relatively uniformly distributed throughout most body-fluids. Binding of the drug to plasma protein is variable, but less than other anti-inflammatory drugs. Some 90 to 100 % of drug may be recovered in the urine within the first day of therapeutic dosing, primarily after hepatic conjugation with glucuronic acid (about 60 %), sulfuric acid (about 35 %), or cysteine (about 3 %); small amounts of hydroxylated and deacetylated metabolites have been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of paracetamol undergoes CYP-mediated N-hydroxylation to form N-acetyl-p-benzoquinone imine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione and thereby is rendered harmless. However, after ingestion of large doses of paracetamol, the metabolite is formed in amounts sufficient to deplete hepatic glutathione and contributes significantly to the toxic effects of overdose **[1]**.

+Therapeutic use of paracetamol

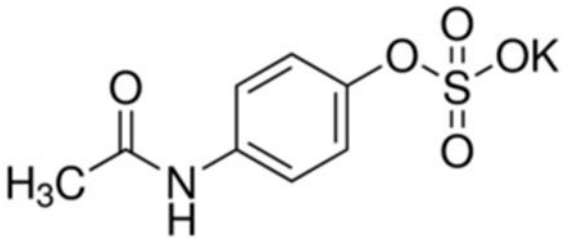
Paracetamol is suitable for analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicate (e.g., those with aspirin hypersensitivity, children with a febrile illness, patients with bleeding disorders). In adults, the conventional oral dose of paracetamol is 325 to 650 mg 4 times-daily or thrice-daily; total daily dose should not exceed 4 grams (2 grams daily for chronic alcoholics). Single doses for children aged 2 to 11 years depend on age and weight (about 10 to 15 mg/ kg); no more than 5 doses should be administered in 24 hours. An injectable preparation is available. Particular attention is warranted due to the availability of a wide variety of prescriptions and non-prescription multi-ingredient medications that represent potentially toxic overlapping sources of paracetamol **[1]**. Paracetamol is a valuable analgesic also sometimes used to control fever. It can be given orally, rectally, and intravenously adds to its usefulness. More recently, paracetamol has been used to affect closure of the patent ductus arteriosus in preterm infants, particularly where ibuprofen has failed or is contraindicated **[2]**. Paracetamol is used to reduce fever and mild to moderate pain. Liver toxicity occurs with excessive doses after prolonged administration (> 48 hours) of therapeutic doses. Rash, fever, thrombocytopenia, and neutropenia have been reported in infants and children. In infants, the peak concentration of paracetamol occurs 60 min after an oral dose. The absorption after a rectal administration is variable and prolonged. Paracetamol is extensively metabolized in the liver, particularly by sulfation with a small amount by glucuronidation. The metabolites and the unchanged drug are excreted by the kidney. The elimination half-life is approximately 3 hours in term infants, 5 hours in preterm infants with < 32 weeks of postmenstrual age, and up to 11 hours in more immature infants. The elimination is prolonged in infants with liver dysfunction **[3]**.



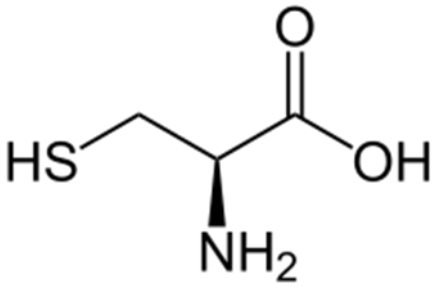
Paracetamol molecular structure (molecular weight = 151,163 grams/mole)



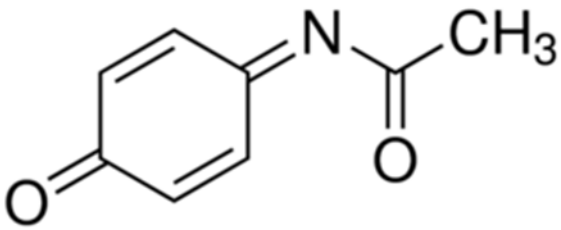
Paracetamol glucuronide molecular structure (molecular weight = 327.29 grams/mole)



Paracetamol sulphate molecular structure (molecular weight = 231.23 grams/mole)



Cysteine molecular structure (molecular weight = 121.16 grams/mole)



N-Acetyl-p-benzoquinone imine molecular structure (molecular weight = 149.15 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: “paracetamol dosing infants, children”, “paracetamol efficacy safety infants, children”, “paracetamol adverse-effects”, “paracetamol metabolism”, “paracetamol pharmacokinetics infants, children”, “paracetamol drug interactions”, “paracetamol prophylaxis infants, children”, “paracetamol treatment infants, children”, “paracetamol trials infants, children”, “paracetamol toxicity infants, children”,

"Paracetamol placental transfer", and paracetamol breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics **[1]**, Neonatal Formulary **[2]**, NEOFAX® by Young and Mangum **[3]**, and The British National Formulary for Children **[4]** are consulted.

Results

Administration schedules of paracetamol to infants and children

Administration to infants [2]

Table 1. Oral paracetamol doses for the treatment of pain or pyrexia

Postmenstrual age (weeks)	Loading dose (mg/kg)	Subsequent doses (mg/kg)	Dosing interval (hours)	Maximum cumulative daily dose (mg/kg)
28 to 32	20	10 to 15	8 to 12	30
≥ 32	20	10 to 15	6 to 8	60

Table 2. Intravenous paracetamol doses for the treatment of pain or pyrexia (given by infusion over 15 minutes)

Postmenstrual age (weeks)	Loading dose (mg/kg)	Subsequent doses (mg/kg)	Dosing interval (hours)	Maximum cumulative daily dose (mg/kg)
28 to 32	20	7.5	8	22.5
33 to 36	20	10	8	40
≥ 37	20	10	5	40

Table 3. Rectal paracetamol doses for the treatment of pain or pyrexia

Postmenstrual age (weeks)	Loading dose (mg/kg)	Subsequent doses (mg/kg)	Dosing interval (hours)	Maximum cumulative daily dose (mg/kg)
28 to 32	---	20	12	40
33 to 37 (and term infants aged < 10 days)	30	15	8	60
Term infants aged ≥ 10 days	30	20	6 to 8	90

Table 4. Dose of paracetamol for the treatment of patent ductus arteriosus

Age (gestational at birth and postnatal age)	Loading dose (mg/kg)	Subsequent doses (mg/kg)	Dosing interval (hours)
23^{+0}-25^{+6} weeks and ≤ 7 days	20	12.5	6
23^{+0}-25^{+6} weeks and > 7 days	20	15	6
≥ 26^{+0} weeks	20	15	6

Table 5. Dose adjustment to be made based on trough paracetamol levels taken just before the third dose is due to be given

Paracetamol level (µg/ml)	Increase dose to 15 mg/kg every 6 hours
< 15	Increase the dose to 15 mg/kg every 6 hours
15 to 25	No change-dose remains 12.5 mg/kg every 6 hours
26 to 34	Decrease the dose to 10 mg/kg every 6 hours
35 to 40	Decrease the dose to 10 mg/kg every 8 hours
> 40	Discontinue the drug

Administration to children [4].

Oral administration for pain and pyrexia with discomfort

Children aged 1 to 2 months. Give: 30 to 60 mg thrice-daily as required, the maximum daily dose to be given in divided doses (maximum dose = 60 mg daily).

Children aged 3 to 5 months. Give: 60 mg 4 times-daily of thrice-daily (maximum = 4 doses daily).

Children aged 6 to 23 months. Give: 120 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 2 to 3 years. Give: 180 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 4 to 5 years. Give: 240 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 6 to 7 days. Give: 240 to 250 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 8 to 9 years. Give: 360 to 375 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 10 to 11 years. Give: 480 to 500 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 12 to 15 years. Give: 480 to 750 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 16 to 17 years. Give: 0.5 to 1 gram 4 times-daily or thrice daily (maximum = 4 doses daily).

Administration by rectum for pain and pyrexia with discomfort

Children aged 1 to 2 months. Give: 30 to 60 mg/kg thrice-daily as required (maximum daily dose to be given in divided doses; maximum = 60 mg/kg daily).

Children aged 3 to 11 months. Give: 60 to 125 mg 4 times-daily or thrice-daily as required (maximum = 4 doses daily).

Children aged 1 to 4 years. Give: 125 to 250 mg 4 times-daily or thrice-daily as required (maximum = 4 doses daily).

Children aged 5 to 11 years. Give: 250 to 500 mg 4 times-daily or thrice-daily (maximum = 4 doses daily).

Children aged 12 to 17 years. Give: 500 mg 4 times-daily or thrice-daily.

Intravenous administration for pain and pyrexia with discomfort

Children with body-weight up to 10 kg. Give: 10 mg/kg 4 times-daily or thrice-daily. The dose should be administered over 15 min (maximum = 30 mg/kg daily).

Children with body-weight of 10 to 50 kg. Give: 15 mg/kg 4 times-daily or thrice-daily. The dose should be administered over 15 min (maximum = 60 mg/kg daily).

Children with body-weight of 50 kg or above. Give: 1 gram 4 times-daily or thrice-daily. The dose should be given over 15 min (maximum = 3 grams daily).

Oral administration for post-operative pain

Children aged 1 month to 5 years. Give: 20 to 30 mg/kg for 1 dose, and then 15 to 20 mg/kg 4 times-daily or thrice-daily (maximum daily dose to be given in divided doses; maximum daily dose = 75 mg/kg).

Children aged 6 to 11 years. Give: 20 to 30 mg/kg (maximum per dose = 1 gram) for 1 dose, and then 15 to 20 mg/kg 4 times-daily or thrice-daily (maximum daily dose to be given in divided doses; maximum daily dose = 75 mg/kg; maximum daily dose = 4 grams).

Children aged 12 to 17 years. Give: 1 gram 4 times-daily or thrice-daily (maximum daily dose = 4 grams).

Administration by rectum for post-operative pain

Children aged 1 to 2 months. Give: 30 mg/kg for 1 dose, and then 15 to 20 mg/kg 4 times-daily or thrice-daily (maximum daily dose to be given in divided doses; maximum daily dose = 75 mg/kg).

Children aged 3 months to 5 years. Give: 30 to 40 mg/kg for 1 dose, and then 15 to 20 mg/kg 4 times-daily or thrice-daily (maximum daily dose to be given in divided doses; maximum daily dose = 75 mg/kg).

Children aged 6 to 11 years. Give: 30 to 40 mg/kg (maximum daily dose = 1 gram for 1 dose, and then 15 to 20 mg/kg 4 times-daily or thrice-daily; the maximum daily dose should be given in divided doses; maximum daily dose = 75 mg/kg, maximum daily dose = 4 grams).

Children aged 12 to 17 years. Give: 1 gram 4 times-daily or thrice-daily (maximum daily dose =4 doses).

Oral prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine (Bexsero®) given as **part of the routine immunisation schedule**

Children aged 2 months. Give: 60 mg, first dose to be given at the time of vaccination, and then 60 mg after 4 to 6 hours, and then 60 mg after 4 to 6 hours, use weight-based doses for preterm infants born at < 32 weeks of gestation and currently weighing < 4 kg – see oral dose for pain and pyrexia discomfort.

Children aged 4 months. Give: 60 mg, first dose to be given at the time of vaccination, and then 60 mg after 4 to 6 hours, and then 60 mg after 4 to 6 hours, use weight-based doses for preterm infants born at < 32 weeks of gestation and currently weighing < 4 kg – see oral dose for pain and pyrexia discomfort.

Bexsero® is a British formulation.

Oral post-immunisation pyrexia in infants

Children aged 2 to 3 months. Give: 60 mg for 1 dose, and then 60 mg after 4 to 6 hours if required.

Children aged 4 to 6 months. Give: 60 mg for 1 dose, and then 60 mg after 4 to 6 hours (maximum 4 doses daily).

Efficacy and safety of paracetamol in infants and children

Paracetamol is the treatment of choice for the closure of the patent ductus arteriosus **[5]**. Paracetamol induces early patent ductus arteriosus closure without significant adverse effects **[6]**. Paracetamol is an effective option in closure of the patent ductus arteriosus **[7]**. Intravenous paracetamol is effective in the closure of the patent ductus arteriosus **[8]**. The clinical efficacy of paracetamol on patent ductus arteriosus closure depends on the duration of treatment and the mode of administration **[9]**. Acetaminophen reduces the risk of post-vaccination fever and fussiness in infants **[10]**. Paracetamol is indicated for use in children of all ages. Overall, clinical evidence qualifies paracetamol 15 mg/kg a safe and effective option for treatment of pain and fever in children **[11]**. Ibuprofen is as or more efficacious than acetaminophen for the treatment of pain and fever in adult and paediatric populations and is equally safe **[12]**. Paracetamol remains the first-choice over-the-counter treatment for analgesia and antipyresis in children **[13]**. Intravenous paracetamol is found to have a similar analgesic efficacy as intravenous dipyrone and they both help to reduce the opioid requirement for postoperative analgesia in paediatric day-case tonsillectomy **[14]**. In children, single doses of ibuprofen (4 to 10 mg/kg) and acetaminophen (7 to 15 mg/kg) have similar efficacy for relieving moderate to severe pain and have similar safety as analgesics or antipyretics **[15]**. Intravenous paracetamol is safe and effective choice for paediatric patients with upper respiratory tract infection presenting with fever **[16]**.

Rare or very rare general adverse-effects caused by paracetamol in infants and children [4]

Thrombocytopenia

Common or very common specific adverse-effects caused by paracetamol in infants and children [4]

With rectal use: Anorectal erythema.

Rare or very rare specific adverse-effects caused by paracetamol in infants and children [4]

With intravenous use: hypersensitivity, hypotension, leukopenia, malaise, neutropenia. With rectal use: angioedema, liver injury, and skin reactions.

Adverse effects induced by paracetamol in infants and children whose frequency is unknown [4]

With intravenous use: flushing, skin reactions, and tachycardia. With oral use: agranulocytosis, bronchospasm, hepatic function abnormal, rash, severe cutaneous adverse reactions. With rectal use: agranulocytosis, blood disorder, and severe cutaneous adverse reactions.

vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this mime, often associated with the onset or right subcostal pain and

tenderness, usually indicates development of hepatic necrosis.

Metabolism of paracetamol in humans

Paracetamol is extensively metabolized and the plasma half-life is 1.5 to 2.5 hours in adults. About 55 % and 30 % of a therapeutic dose is excreted in the urine as glucuronide and sulphate conjugates, respectively, whereas mercapturic acid and cysteine conjugates (representing conversion to a potentially toxic intermediate metabolite) each account for some 4 % of the dose. Paracetamol metabolism is age-dependent and dose-dependent. In 8 healthy subjects who received paracetamol at a dose of 20 mg/kg the mean recovery of paracetamol, paracetamol sulphate, and paracetamol glucuronide in the urine is 5.0 %, 32.3 %, and 54.7 %, respectively. In infants and young children, the glucuronidation and sulfation of paracetamol are deficient **[17]**. Metabolism and urinary excretion of paracetamol following an oral dose of 1 gram was investigated during 24 hours following the administration. The mean±SEM for the cumulative percentage of the dose excreted in urine for total paracetamol is 38.39±4.35 %. The percentage of free paracetamol excreted in the urine is 19.59±2.34 % and that of conjugated paracetamol it is 18.57±2.34 %. The percentage of conjugate paracetamol is 54.1±6.34 in males and 29.8±3.67 % in females. The rate of excretion of paracetamol was less than 1 mg/min/kg in all the volunteers for total, free and conjugated drug. The percentage of conjugated paracetamol in male and female is 15.71 % and 8.73 % respectively, indicating that the formation-rate of these metabolites is higher in males **[18]**. Paracetamol is metabolised via several metabolic pathways, including glucuronidation, sulfation, oxidation, hydroxylation, and deacetylation. Hepatic and other organ damage may occur, especially in overdose, because of the accumulation of a toxic metabolite **[19]**. Paracetamol tablets were administered to children and unchanged paracetamol, paracetamol sulphate and paracetamol glucuronide were recovered in the urine at the following percentages: 2.1, 52.1, and 42.0, respectively **[20]**.

Pharmacokinetics of paracetamol in infants

van Lingen et al. **[21]** studied the pharmacokinetics of paracetamol in 28 preterm infants who were clustered into two groups. Group A consisted in 21 infants with a postmenstrual age of 28 to 32 weeks and weighed 1,280±284 grams and in 7 infants of group B with a postmenstrual age of 32 to 36 weeks and weighed 1,786±323 grams. All infants were treated with a single rectal dose of paracetamol of 20 mg/kg.

Table 6. Pharmacokinetic parameters of paracetamol which are obtained in 21 infants of group A and in 7 infants of group B. Figures are the mean±SD and (range), by van Lingen et al. **[21]**.

Parameter	Infants of group A	Infants of group B	*P-value
Peak concentration (µg/ml)	12.5±2.9 (7.5 – 18.0)	7.5±4.0 (1.5 – 13.6)	0.001
Tmax (h)	3.9 (0.8 – 10.5)	5.1 (1.0 – 9.5)	NS
Elimination half-life (h)	11.0±5.7 (3.5 – 25.2)	4.38±1.2 (3.6 – 6.8)	0.011
AUC (µg/h/ml)	95.1±28.0 (29.0 – 161)	71.7±41.7 (17.5 – 135)	0.046
Total body clearance (L/h)	0.10±0.04 (0.03 – 0.17)	0.56±0.66 (0.13 – 1.70)	0.04

Tmax = time to reach the peak concentration. NS = Not significant. *Student t test.

This table shows that paracetamol is eliminated faster in infants of group B, the AUC is lower in infants of group B and the total body clearance is greater in infants of group B. Paracetamol is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation.

Walson et al. **[22]** investigated the pharmacokinetics of paracetamol in 27 infants aged 3 to 36 months. Paracetamol was administered for fever, pain, or post-immunization prophylaxis of fever and discomfort and infants received 10 to 15 mg/kg paracetamol as the rectal suppository or oral elixir.

Table 7. Demographic characteristics of 27 infants. Figures are the mean±SD, by Walson et al. **[22]**.

				Sex and umber		Race and number		
Treatment	**Age (month)**	**Weigh (kg)**	**Dose (mg/kg)**	**Male**	**Female**	**White**	**Black**	**Biracial**
Elixir	10.0±6.3	8.6±2.3	12.14±1.87	7	5	5	5	2
Suppository	12.4±8.1	9.4±2.4	12.31±1.89	7	8	4	11	0

Figures are not statistically significant.

Table 8. Least squares pharmacokinetic estimates based on non-log-transformed values from 26 study infants with at least 3 postdose concentrations, by Walson et al. **[22]**.§

Treatment	**Ke (h^{-1})**	**Elimination half-life (h)**	**Tmax (h)**	**AUC_{0-t} (µg*h/ml)**	**$AUC_{0-\infty}$ (µg*h/ml)**	**Total body clearance (L/h)**	**Peak conc. (µg/ml)**
Elixir	0.39	1.84	1.16	23.36	27.25	3.56	7.65
Suppository	0.34	2.10	1.17	20.45	22.03	4.25	5.68
***P-value**	0.17	0.14	0.98	0.22	0.24	0.38	0.06

Ke = Elimination rate constant. Tmax = time to reach the peak concentration.

§There were 8.1±2.2 and 9.3±1.4 samples collected from subjects who received 12.14±1.87 mg/kg of elixir and 12.31±1.89 mg/kg suppository. *ANOVA.

This table shows that the comparison of all values between the elixir and the suppository are not significantly different.

Hahn et al. **[23]** explored the pharmacokinetics of paracetamol in 33 children, aged 0.2 to 11.0 years. Paracetamol suppositories were administered at a dose of 25 mg/kg 4 times-daily for a maximum of 5 days.

Table 9. Demographic characteristics of children and treatment details. Figures are the minimum, maximum, mean, and ±SD, by Hahn et al. **[23]**.

Value	**Age (years)**	**Weight (kg)**	**BMI (kg/m^2)**	**BSA (m^2)**	**Dose (mg/kg)**	**Number of doses**	**LOT (h)**	**N. of saliva and blood samples**
Minimum	0.2	5.2	13.9	0.28	20.8	5	19.5	5
Maximum	11.0	38.0	17.4	1.32	27.0	17	95.6	24
Mean	5.3	20.0	15.7	0.76	24.1	4.0	63.0	15.9
±SD	3.6	10.2	1.0	0.33	1.8	12.0	24.4	5.2

BMI = body mass index. BSA = body surface area. LOT = length of treatment, determined as the time from first to last administration of paracetamol suppositories.

Table 10. Pharmacokinetic parameters of paracetamol which are obtained in 33 children, aged 0.2 to 11.0 years, who received paracetamol suppositories at a dose of 25 mg/kg 4 times-daily. Figures are the minimum, maximum, ±SD and the mean, by Hahn et al. **[23]**.

Value	**Ka (h^{-1})**	**Tlag (h)**	**Ke (h^{-1})**	**Elimination half-life (h)**	**DV/F (L/kg)**	**Tmax (h)**	**Peak conc. (µg/ml)**	**TBC/F (L/kg/h)**	**T (h)**	**$Conc._{ss}$ (µg/ml)**	**$TConc._{ss}$ (h)**
Minimum	0.19	0.0	0.06	1.07	0.50	0.43	6.99	0.17	4.38	6.69	3.52
Maximum	9.29	1.60	0.65	11.46	2.74	5.26	19.05	0.56	8.50	39.91	37.81
Mean	1.38	0.52	0.0	3.45	1.32	2.37	10.71	0.31	5.85	12.22	11.08
±SD	2.22	0.42	0.17	2.59	0.66	1.10	3.09	0.10	0.84	5.20	8.55

Ka = Absorption rate constant. Tlag = lag time. DV = distribution volume. Tmax = time to reach the peak concentration. TBC = total body clearance. T = dosing interval. $Conc._{ss}$ = concentration at the stead-state. $TConc._{ss}$ = time to reach 90 % of the concentration at the steady-state. F = bioavailability.

This table shows that paracetamol administered as suppositories is rapidly absorbed, the lag time is short, the elimination rate constant is short, the distribution volume is similar to the water volume, the time to reach the peak concentration is short, the total body clearance is limited, the dosing interval is short, the concentration at the steady-state is high and the time to reach 90 % of the concentration at the steady is short, and there is a remarkable interindividual variability in the pharmacokinetic parameters. Such variability is accounted by the wide variation of the demographic characteristics of children. The elimination half-life of paracetamol is longer in infants (see tables 6) than that in children. Paracetamol is cleared from the body by metabolism and renal route and these elimination pathways increase with infant maturation and child development.

Interaction of drugs with paracetamol

The paracetamol metabolite N-acetyl-p-benzoquinone imine causes hepatotoxicity and the co-administration of paracetamol with warfarin increases the anticoagulant effects. In addition, the absorption of paracetamol is depending by the gastric emptying and the drugs that alter gastric emptying change the pharmacokinetics of paracetamol **[24]**. When paracetamol and warfarin are co-administered the number of fatal bleeds is 4.6-fold higher compared to the administration of warfarin alone **[25]**. An interaction is found between paracetamol and warfarin, between paracetamol and valsartan, and between paracetamol and phenytoin and these interactions cause abnormal blood values **[26]**. Highly protein-bound drugs such as phenylbutazone, phenytoin, or warfarin can compete with the common binding sites of paracetamol **[27]**.

Prophylaxis with paracetamol in infants and children

The rate of patent ductus arteriosus is significantly lower in the paracetamol-treated group compared to the control group (13.6 % versus 38.2 %, $p < 0.001$) **[28]**. The prophylactic administration of paracetamol decreases the immune response to certain pneumococcal serotypes **[29]**. Paracetamol may interfere with immune responses to pneumococcal antigens **[30]**. The percentage of children with temperature of ≥ 38 C° after at least one dose was significantly lower in the prophylactic paracetamol group (42 %) after primary vaccination and 36 % after booster vaccination than in the no prophylactic paracetamol group 66 % after primary vaccination and 58 % after booster vaccination **[31]**.

Treatment of infants and children with paracetamol

Paracetamol is as effective as ibuprofen in the closure of patent ductus arteriosus **[32]**. Intravenous paracetamol is used as an alternative drug for the closure of the patent ductus arteriosus **[33]**. Paracetamol serum concentrations ranges from 8 to 64 µg/ml after 8 to 12 doses of intravenous paracetamol and these concentrations of paracetamol are effective and safe **[34]**. Plasma paracetamol concentration should be 10 to 20 µg/ml to achieve antipyretic and analgesic effects **[35]**. Clinical evidence qualifies paracetamol 15 mg/kg a safe and effective option for treatment of pain and fever in children **[36]**. Paracetamol achieves effective antipyresis and provides early symptomatic improvement in children with febrile illness without prolongation of fever duration or excessive adverse effects **[37]**.

Trials with paracetamol in infants and children

Current follow-up results on paracetamol-exposed very preterm infants may not be alarming suggesting that paracetamol administration shortly after birth is not associated with common adverse-consequences **[38]**. Paracetamol (12.5 mg/kg per dose) and ibuprofen (5 mg/kg per dose) 6 times-daily for 3 days, regardless of the initial loading medication, is more effective than monotherapy in lowering fever in infants and children **[39]**. Infants who are treated with paracetamol no long-term adverse reactions of early intravenous paracetamol were detected two years later **[40]**.

Toxicity caused by paracetamol in infants and children

Caution should be used when paracetamol is administered to the newborns. In the event of an overdose, careful patient monitoring and personalization of post-overdose procedures are recommended **[41]**. A 55 day old infant was accidentally given 136 mg/kg paracetamol. Treatment was with activated

charcoal, supportive care, and N-acetylcysteine **[42]**. Decreased paraoxonase-1 activity is associated with increased oxidative stress in children treated with acetaminophen intoxication **[43]**. Administration of supra-therapeutic doses of paracetamol is common and risk increased with child's age. Knowledge on calculating the weight appropriate paracetamol dose is poor **[44]**. Hepatotoxicity may occur for lower doses of intravenous paracetamol compared to oral ingestion and a dose < 150 mg/kg of intravenous paracetamol should be used to define treatment following overdose in a child **[45]**. Therapeutic doses of paracetamol in infants and young children should be a lot lower than that previously appreciated **[46]**.

Transfer of paracetamol across the human placenta

Paracetamol exposure in maternal venous blood was similar to foetal venous umbilical cord blood **[47]**. Foetal paracetamol pharmacokinetics in the foetus parallels that in the mother suggesting that placental transfer is flow limited **[48]**. Paracetamol (1 g orally) was given to each of 10 healthy pregnant women undergoing normal vaginal delivery. Following delivery, there was no significant difference in the serum concentration of paracetamol in the mother and the foetus, the mean value being 5.9±2.1 and 7.9±2.2 mg/ml, respectively **[49]**. The percentage placental transfer of paracetamol was 45 % (maternal-to-foetal and foetal-to-maternal). For paracetamol sulphate, the transfer was 39 % (maternal-to-foetal) and 28 % (foetal-to-maternal), while the paracetamol glucuronide transfer was 34 % (maternal-to-foetal) and 25 % (foetal-to-maternal). During placenta perfusions with the metabolites slight conversion (3.5 to 4.1 %) to paracetamol is observed. In conclusion, paracetamol crosses the placental barrier rapidly via passive diffusion **[50]**.

Paracetamol migration into the breast-milk

Paracetamol was administered to nursing mothers. The drug passes rapidly into the breast-milk and the milk to plasma concentration ratio is approximately the unity. The estimated maximum dose to the neonate was 1.85 % of the weight-adjusted maternal oral dose of paracetamol 1 gram **[51]**. Breast-milk and plasma levels of paracetamol were monitored in 3 lactating women after ingestion of a single 500 mg of paracetamol. The paracetamol concentrations are consistently lower in breast-milk, with mean milk to plasma AUC ratio of 0.76. This value is in close agreement with the breast-milk to plasma partition ratio of 0.81 found in vitro. The half-life of paracetamol in plasma and breast-milk is almost identical, with an overall mean of 2.7 h. As less than 0.1 % of the maternal dose would be present in 100 ml of breast milk **[52]**.

Discussion

Paracetamol (acetaminophen) is the active metabolite of phenacetin. Paracetamol has analgesic and antipyretic effect. It is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. Paracetamol may be administered orally, rectally, and intravenously and the bioavailability is good **[1]**. In infants, the oral dosing of paracetamol consists in a loading dose of 20 mg/kg followed by subsequent dose of 10 to 15 mg/kg twice-daily or thrice-daily **[2]**. In children, the paracetamol dosing varies according to the child age and the child body weight **[4]**. Paracetamol has been found efficacy and safe in infants and children **[5-16]**. Paracetamol is efficacy and safe in the closure of the patent ductus arteriosus without inducing adverse-effects **[5-9]**, in reducing fever and fussiness in post-vaccinated infants **[10]**, and paracetamol is a safe and effective agent to treat pain and fever **[11, 13]**. Ibuprofen is more efficacious than paracetamol for the treatment of pain and fever, but it is equally safe **[12]**. Intravenous paracetamol has similar analgesic efficacy as intravenous dipyrone **[14]**. In children, a dose of 4 to 10 mg/kg of ibuprofen has similar analgesic and antipyretic activities of 7 to 15 mg/kg paracetamol **[15]** and intravenous paracetamol is a safe and effective agent to treat paediatric patients with upper respiratory tract infection presenting with fever **[16]**. Paracetamol may induce adverse effects **[4]**. Paracetamol is extensively metabolized and its major metabolites are paracetamol glucuronide and paracetamol sulphate and minor metabolites are mercapturic acid and cysteine conjugates and N-acetyl-p-benzoquinone imine, the last is formed by CYP enzymes. This metabolite reacts with the sulfhydryl groups in glutathione and thereby is harmless. The metabolism of paracetamol is dose and

gender dependent, the conjugate metabolites of paracetamol are higher in males than in females and paracetamol and its metabolites are excreted in the urine **[17-20]**. The pharmacokinetics of paracetamol have been studied in infants **[21, 22]** and in children **[23]**. The elimination half-life of paracetamol is 11.0 hours in more immature preterm infants and 4.38 hours in less immature preterm infants. The total body clearance of paracetamol is 0.10 L/h in younger preterm infants and 0.56 L/h in older preterm infants **[21]**. In children, the elimination half-life and the total body clearance of paracetamol are 3.45 hours and 0.31 L/kg/h, respectively **[23]**. Paracetamol is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation and child development and this consideration explains the longer half-life and the smaller total body clearance observed in infants than children. Paracetamol interacts with drugs **[24-27]**. The co-administration of paracetamol and warfarin increases the risk of blending caused warfarin **[24, 25]**. Paracetamol interacts with warfarin, valsartan, and phenytoin and these interactions cause abnormal blood values **[26]**. Highly protein-bound drugs such as phenylbutazone, phenytoin, or warfarin compete with the binding sites of paracetamol **[27]**. The prophylaxis with paracetamol has been studied in infants and children **[28-31]**. Paracetamol close the patent ductus arteriosus **[28]**, prophylactic paracetamol decreases the immune response to certain pneumococcal serotypes **[29]**, paracetamol may interfere with immune response to pneumococcal antigens **[30]**, and paracetamol decreases the fever in children after vaccination **[31]**. The treatment with paracetamol has been reported in infants and children **[32-37]**. Paracetamol is efficacy as ibuprofen in closing the patent ductus arteriosus **[32]**, intravenous paracetamol closes the patent ductus arteriosus **[33]**, paracetamol serum concentrations of 8 to 64 µg/ml when administered for 8 to 12 doses is effective and safe **[34]**, paracetamol has antipyretic and analgesic effects at concentrations of 10 to 20 mg/ml **[35]**, paracetamol produces analgesic and antipyretic effects **[36, 37]**. The trials with paracetamol have been described in infants and children **[38-40]**. Paracetamol administered to very preterm infants is not associated with adverse-consequences **[38]**, paracetamol administered at a dose of 12.5 mg/kg and ibuprofen administered at a dose of 5 mg/kg 6 times-daily for 3 days are more effective than the monotherapy in lowering fever in infants and children **[39]**, and infants treated with paracetamol did not report adverse-reactions two years later **[40]**. The toxicity caused by paracetamol has been reported in infants and children **[41-46]**. Overdose of paracetamol may induce toxicity and the patient should be monitored and personalization of post-overdose procedures are recommending **[41]**, and the overdose of paracetamol should be treated with activated charcoal, supportive care, and N-acetylcysteine **[42]**. Paracetamol intoxication is associated to decreased paraoxonase-1 activity **[43]**. Administration of supra-therapeutic doses of paracetamol is common and the risk increases with child's age **[44]**. Hepatotoxicity may occur when paracetamol is administered at a dose < 150 mg/kg **[45]**. The therapeutic doses of paracetamol in infants and children should be lower than those previously appreciated **[46]**. The transfer of paracetamol across the human placenta has been studied in pregnant women at vaginal delivery **[47-49]** and in-vitro using the perfused placenta **[50]**. Paracetamol equilibrates between the maternal and foetal compartments. Paracetamol sulfate and paracetamol glucuronide are formed by the placenta and their transfer-rates are lower than that of unchanged paracetamol **[50]**. Paracetamol migrates into the breast milk where achieves significant amounts **[51, 52]**.

In conclusion, paracetamol (acetaminophen) is used to treat pain and fever. It is a nonselective cyclooxygenase inhibitor which acts at the peroxidase site of the enzyme and is thus distinct among the nonsteroidal anti-inflammatory drugs. Paracetamol may be administered orally, rectally, or intravenously and the bioavailability is good. In infants, the oral dosing of paracetamol consists in a loading dose followed by subsequent doses and in children the dose varies with the child age and child body-weight. Paracetamol is extensively metabolized; the main metabolites are paracetamol glucuronide and paracetamol sulphate and the minor metabolites are mercapturic acid and cysteine conjugates, and N-acetyl-p-benzoquinone imine. The last is formed by CYP enzymes, it is a reactive metabolite and reacts

with the sulfhydryl group in glutathione and thereby is rendered harmless. Paracetamol and its metabolites are excreted in the urine. The pharmacokinetics of paracetamol has been extensively studied in infants and in children. The elimination half-life of paracetamol is shorter in children than in infants as paracetamol is eliminated by metabolism and renal route and both elimination pathways increase with infant maturation and child development. Paracetamol is fond efficacy and safe in infants and children but it may induce adverse-effects. Paracetamol interacts with drugs, and the prophylaxis, treatment, and trials have been studied in infants and children. Paracetamol crosses the human placenta and migrates into the breast-milk in significant amounts. The aim of this study is to review the clinical pharmacology of paracetamol in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

References

1. Grosser T, Smyth EM, FitzGerald GA. (2018) Pharmacotherapy of Inflammation, Fever, Pain, and Gout. In The Goodman Gilman's. The Pharmacological Basis of the Therapeutics, Brunton Hilal-dandan LL, Knollmann BC, editors. Mc Graw Hill, 13th Edition, USA, New York 685-709.
2. Neonatal Formulary. (2020) Paracetamol. Oxford University Press. 8th Edition, Great Clarendon Street, Oxford, OX2, 6DP, UK 600-604.
3. Young TE, Mangum B. NEOFAX®. (2010) Acetaminophen. Thomas Reuters Clinical Editorial Staff, 23rd Edition, Montvale, USA 204-205.
4. The British national formulary for children. (2019-2020) Paracetamol. Macmillan, 78th Edition, Hampshire International Business Park, Hampshire, Lime Three Way, Basingstoke, Hampshire, UK, 278-279.
5. Mahmoud NS, Asklany H. (2021) Paracetamol for closure of patent ductus arteriosus in preterm babies born before 32-week gestational age: academic unit experience. J Clin Neonatol. 10(2); 79-87.
6. Xiao Y, Liu H, Hu R, You Q, Zeng M, Jiang X. (2019) Efficacy and Safety of Paracetamol for Patent Ductus Arteriosus Closure in Preterm Infants: An Updated Systematic Review and Meta-Analysis. Front Pediatr. 7(2): 568-590.
7. Tofe I, Ruiz-González MD, Cañete MD, Pino A, Rosa Rueda L, et al. (2018) Efficacy of Paracetamol in Closure of Ductus Arteriosus in Infants under 32 Weeks of Gestation. Front Pediatr. 6(2): 25.
8. Valerio E, Valente MR, Salvadori S, Frigo AC, Baraldi E, et al. (2016) Intravenous paracetamol for PDA closure in the preterm: a single-center experience. Eur J Pediatr. 175(7): 953-966.
9. El-Khuffash A, Jain A, Corcoran D, Shah PS, Hooper CW, Brown N, et al. (2014) Efficacy of paracetamol on patent ductus arteriosus closure may be dose dependent: evidence from human and murine studies. Pediatr Res. 76(3): 238-244.
10. Jackson LA, Peterson D, Dunn J, Hambidge SJ, Dunstan M, Starkovich P, et al. (2011) A randomized placebo-controlled trial of acetaminophen for prevention of post-vaccination fever in infants. PLoS One. 6(6): e20102.
11. de Martino M, Chiarugi A. (2015) Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther. 4(2): 149-168.
12. Pierce CA, Voss B. (2010) Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother. 44(3): 489-506.
13. Cranswick N, Coghlan D. (2000) Paracetamol efficacy and safety in children: the first 40 years. Am J Ther. 7(2):135-141.

14. Kocum AI, Sener M, Caliskan E, Bozdogan N, Micozkadioglu D, Yilmaz I, et al. (2013) Intravenous paracetamol and dipyrone for postoperative analgesia after day-case tonsillectomy in children: a prospective, randomized, double blind, placebo controlled study. Braz J Otorhinolaryngol. 79(1): 89-94.
15. Perrott DA, Piira T, Goodenough B, Champion GD. (2004) Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. Arch Pediatr Adolesc Med. 158(6): 521-526.
16. Choi SJ, Moon S, Choi UY, Chun YH, Lee JH, Rhim JW, et al. (2018) The antipyretic efficacy and safety of propacetamol compared with dexibuprofen in febrile children: a multicenter, randomized, double-blind, comparative, phase 3 clinical trial. BMC Pediatr. 18(1): 201.
17. Prescott LF. (1980) Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol. 10: 291S-298S.
18. Raza AA, Jabeen A, Nawaz R. (1999) Influence of gender of paracetamol metabolism. J Animal Plant Sci. 9(1-2): 1-3.
19. Zhao L, Pickering G. (2011) Paracetamol metabolism and related genetic differences. Drug Metab Rev. 43(1): 41-52.
20. Peterson RG, Rumack BH. (1978) Pharmacokinetics of acetaminophen in children. Pediatrics. 62(5 Pt 2 Suppl): 877-879.
21. van Lingen RA, Deinum JT, Quak JM, Kuizenga AJ, van Dam JG, et al. (1999) Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. Arch Dis Child Fetal Neonatal Ed. 80(1): F59-F63.
22. Walson PD, Halvorsen M, Edge J, Casavant MJ, Kelley MT. (2013) Pharmacokinetic comparison of acetaminophen elixir versus suppositories in vaccinated infants (aged 3 to 36 months): a single-dose, open-label, randomized, parallel-group design. Clin Ther. 35(2): 135-140.
23. Hahn TW, Henneberg SW, Holm-Knudsen RJ, Eriksen K, Rasmussen SN, et al. (2000) Pharmacokinetics of rectal paracetamol after repeated dosing in children. Br J Anaesth. 85(4): 512-519.
24. Toes MJ, Alison JL, Prescott L. (2005) Drug Interactions with Paracetamol. Am J Ther. 12(1): 56-66.
25. Launiainen T, Sajantila A, Rasanen I, Vuori E, Ojanperä I. (2010) Adverse interaction of warfarin and paracetamol: evidence from a post-mortem study. Eur J Clin Pharmacol. 66(1): 97-103.
26. Oldenburg LIK, Dalhoff KP, Sandoval LØ, Vermehren C. (2020) The Risk of Drug-Drug Interactions with Paracetamol in a Population of Hospitalized Geriatric Patients. J Pharm (Cairo). 1354209.
27. Klotz U. (1983) Interactions of analgesics with other drugs. Am J Med. 75(5A): 133-138.
28. Höck M, Brunner B, Rier V, Thöni S, Trawöger R, Geiger R, et al. (2020) Prophylactic low-dose paracetamol administration associated with lowered rate of patent ductus arteriosus in preterm infants - Impact on outcome and pain perception. Pediatr Neonatol. 61(1): 84-91.
29. Koufoglou E, Kourlaba G, Michos A. (2021) Effect of prophylactic administration of antipyretics on the immune response to pneumococcal conjugate vaccines in children: a systematic review. Pneumonia (Nathan). 13(1): 7.
30. Wysocki J, Center KJ, Brzostek J, Majda-Stanislawska E, Szymanski H, et al. (2017) A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. Vaccine. 35(15): 1926-1935.
31. Prymula R, Siegrist C-A, Chlibek R, Zemlickova H, Vackova M, et al. (2009) Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 374(9698): 1339-1350.
32. Ohlsson A, Shah PS. (2018) Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 4(4): CD010061.
33. Oncel MY, Yurttutan S, Degirmencioglu H, Uras N, Altug N, et al. (2013) Intravenous paracetamol

treatment in the management of patent ductus arteriosus in extremely low birth weight infants. Neonatology. 103(3): 166-169.

34. van Ganzewinkel C-J J, Mohns T, van Lingen RA, Derijks LJ, Andriessen P. (2012) Paracetamol serum concentrations in preterm infants treated with paracetamol intravenously: a case series. J Med Case Rep. 6: 1.
35. Arana A, Morton NS, Hansen TG. (2001) Treatment with paracetamol in infants. Acta Anaesthesiol Scand. 45(1): 20-29.
36. de Martino M, Chiarugi A. (2015) Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther. 4(2): 149-168.
37. Gupta H, Shah D, Gupta P, Sharma KK. (2007) Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo-controlled trial. Indian Pediatr. 44(12): 903-911.
38. Juujärvi S, Saarela T, Hallman M, Aikio O. (2021) Trial of paracetamol for premature newborns: five-year follow-up. J Matern Fetal Neonatal Med. 1-3.
39. Sarrell EM, Wielunsky E, Cohen HA. (2006) Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. Arch Pediatr Adolesc Med. 160(2): 197-202.
40. Juujärvi S, Kallankari H, Pätsi P, Leskinen M, Saarela T, Hallman M. (2019) Follow-up study of the early, randomised paracetamol trial to preterm infants, found no adverse reactions at the two-years corrected age. Acta Paediatr. 108(3): 452-458.
41. Locci C, Cuzzolin L, Capobianco G, Antonucci R. (2021) Paracetamol overdose in the newborn and infant: a life-threatening event. Eur J Clin Pharmacol. 77(6): 809-815.
42. Isbister GK, Bucens IK, Whyte IM. (2001) Paracetamol overdose in a preterm neonate. Arch Dis Child Fetal Neonatal Ed. 85(1): F70- F72.
43. Karadas S, Aslan M, Gonullu H, Kati C, Duran L, et al. (2014) Acetaminophen intoxication is associated with decreased serum paraoxonase and arylesterase activities and increased lipid hydroperoxide levels. Hum Exp Toxicol. 33(11): 1134-1140.
44. Ramanayake RPJC, Jayasinghe LR, De Silva AHW, Wijesinghe WATA, Kanaganayagam N. (2012) Knowledge and practices of paracetamol administration among caregivers of pediatric age group patients. J Family Med Prim Care. 1(1): 30-33.
45. Berling I, Anscombe M, Isbister GK. (2012) Intravenous paracetamol toxicity in a malnourished child. Clin Toxicol (Phila). 50(1): 74-76.
46. Penna A, Buchanan N. (1991) Paracetamol poisoning in children and hepatotoxicity. Br J Clin Pharmacol. 32(2): 143-149.
47. Mian P, Allegaert K, Conings S, Annaert P, Tibboel D, Pfister M, et al. (2020) Integration of Placental Transfer in a Fetal-Maternal Physiologically Based Pharmacokinetic Model to Characterize Acetaminophen Exposure and Metabolic Clearance in the Fetus. Clin Pharmacokin. 59(2): 911-925.
48. Nitsche JF, Patil AS, Langman LJ, Penn HJ, Derleth D, et al. (2017) Transplacental Passage of Acetaminophen in Term Pregnancy. Am J Perinatol. 34(6): 541-543.
49. Rani MAN, Joseph T, R Narayanan R. (1989) Placental transfer of paracetamol. J Indian Med Assoc. 87(8): 182-183.
50. Conings S, Tseke F, Van den Broeck A, Qi B, Paulus J, Amant F, et al. (2019) Transplacental transport of paracetamol and its phase II metabolites using the ex vivo placenta perfusion model. Toxicol Appl Pharmacol. 370(5): 14-23.
51. Notarianni LJ, Oldham HG, Bennett PN. (1987) Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. Br J Clin Pharmacol. 24(1): 63-67.
52. Bitzén PO, Gustafsson B, Jostell KG, Melander A, Wåhlin-Boll E. (1981) Excretion of paracetamol in human breast milk. Eur J Clin Pharmacol. 20(2): 123-125.