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Clinical Pharmacology of Aspirin in Infants and Children

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Abstract

Aspirin is used to treat fever, pain, and inflammation. Oral aspirin is rapidly absorbed, partially from the stomach, but mostly from the upper small intestine, and the absorption-rate is determined by disintegration and dissolution rates of tablets. In adults, the oral analgesic-antipyretic dose is 325 to 1,000 mg 4- to 6-times-daily and aspirin oral dose to treat inflammation and rheumatic fever is 4 to 8 grams daily. Oral aspirin is used to treat the Kawasaki disease and to prevent thrombus formation in infants and children. Aspirin has been found efficacy and safe in infants and children and aspirin has been used to close the patent ductus arteriosus, to reduce neurobehavioral difficulties, and to treat inflammation in infants and children. Aspirin is extensively metabolized into salicylic acid, gentisic acid, salicyluric acid, and conjugation with glucuronic acid. In normal-weight children, the elimination half-life of aspirin, salicylic acid, gentisic acid and salicyluric acid, is 0.195, 0.294, 0.193, and 0.171 hours, respectively, but the half-life of these compounds varies in underweight children. The treatment and trials with aspirin have been extensively studied in infants and children, aspirin interacts with drugs, and aspirin exerts different effects on the human brain. Aspirin freely crosses the human placenta and poorly migrates into the breast-milk. The aim of this study in to review the published data of aspirin dosing, efficacy and safety, effects, pharmacokinetics, treatment, trails in infants and children, and aspirin metabolism, placental transfer and migration into the breast-milk.

Keywords: Aspirin; Efficacy and safety; Effects; Metabolism; Pharmacokinetics; Treatment; Trials; Drug-Interaction; Human Brain; Placenta; Breast-Milk; Infants; Children

Introduction

Aspirin and other salicylates

The salicylates include aspirin, salicylic acid, methyl salicylate, diflunisal, salsalate (an unapproved marketed drug in the US), olsalazine, sulfasalazine, choline magnesium trisalicylate (an unapproved marketed drug in the US), magnesium salicylate, mesalamine, and salicylamide (a carboxamide derivative of salicylic acid contained as an ingredient in some over the count combination pain relievers). Salicylic acid is so irritating that it can only be used externally; therefore, the various derivatives of this acid have been synthetized for systemic use. For example, aspirin is the acetate ester of salicylic acid. Aspirin is a widely consumed analgesic, antipyretic, and anti-inflammatory agent. Because aspirin is so available, the possibility of misuse and serious toxicity is underappreciated, and it remains a cause of fatal poisoning in children [1].

Mechanism of action of salicylates

The effects of aspirin are largely caused by its capacity to acetylate proteins as described in irreversible cyclooxygenase inhibition by aspirin. Other salicylates generally act by virtue of their content of salicylic acid, which is a relatively weak inhibitor of the purified cyclooxygenase (COX) enzymes. Salicylic acid may also suppress inflammatory upregulation of COX-2 by interfering with transcription factor binding to the COX-2 promoter [1].

Absorption, distribution, metabolism, and elimination of salicylates

Absorption: Orally ingested salicylates are absorbed rapidly, partially from the stomach, but mostly from the upper small intestine. The plasma level is reached in about 1 hour. The rate of absorption is determined by disintegration and dissolution rates of the tablets administered the pH at the mucosa surface, and gastric empting time. Even though salicylate is more ionized as the pH is increased, a rise in pH also increases the solubility of salicylate. The presence of food delays absorption of salicylates. Rectal absorption of salicylate usually is slower than oral absorption and is incomplete and inconsistent. Salicylic acid is absorbed rapidly from the intact skin, especially when applied in oil liniment or ointments, and systemic poisoning has occurred from its application to large areas of skin. Methyl salicylate likewise is speedily absorbed when applied cutaneously; however, its gastrointestinal absorption may be delayed many hours, making gastric lavage effective for removal even in poisoning that present late after oral ingestion. Enteric coating delays and reduces the bioavailability of aspirin by roughly half and reduces absorption more variable in the presence of food which is likely the cause of "pseudo-resistance" to aspirin [1].

Distribution: After absorption, salicylates are distributed throughout most body tissues and transcellular fluids, primarily by pH-dependent processes. Salicylates are transported actively out the cerebrospinal fluid across the choroid plexus. The drugs readily cross the placental barrier. Ingested aspirin mainly is absorbed as such, but some enters the systemic circulation as salicylic acid after hydrolysis by esterases in the gastrointestinal mucosa and liver. Roughly 80 to 90% of the salicylate in plasma is bound to proteins, especially albumin; the proportion of the total that is bound declines as plasma concentrations increase. Hypoalbuminemia, as may occur in rheumatoid arthritis, is associated with a proportionality higher level of free salicylate in the plasma. Salicylate competes with a variety of compounds for plasma protein-binding sites; these include thyroxine, triiodothyronine, penicillin, phenytoin, sulfinpyrazone, bilirubin, uric acid, and other nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen. Aspirin is bound to a more limited extent; however, it acetylates human plasma albumin in-vivo by reaction with the amino group of lysine and may change the binding of other drugs to albumin. Aspirin also acetylates other plasma and tissue proteins, but there is no evidence that this contributes to clinical efficacy or adverse-effects [1].

Metabolism and Excretion: Aspirin is rapidly deacetylated to form salicylic acid by spontaneous hydrolysis or esterases located in the intestinal wall, red blood cells, and the liver. The three chief metabolic products are salicyluric acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acyl glucuronide. Salicylates and their metabolites are excreted in the urine. The excretion of free salicylates is variable and depends on the dose and the urinary pH, for example, the clearance of salicylate is about four times as great at pH 8 as at pH 6, and it is well above the tubular reabsorption, whereas the opposite is true in oliguria. The plasma elimination half-life for aspirin is about 20 min, and for salicylate is 2 to 3 hours at antiplatelet doses, rising to 15 to 30 hours

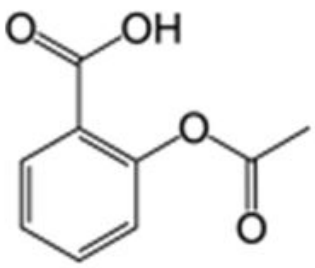
at high therapeutic doses or when there is intoxication. This dose-dependent elimination is the result of the limited capacity of the liver to form salicyluric acid and the phenolic glucuronide, resulting in a larger proportion of unchanged drug being excreted in the urine at higher doses. Salicylate metabolism shows high intersubject variability due to the variable contribution of different metabolic pathways. Women frequently exhibit higher plasma concentrations, perhaps due to lower intrinsic esterases activity and gender differences in hepatic metabolism. Salicylate clearance is reduced and salicylate exposure is significantly increased in the elderly. The plasma concentration of salicylate is increased by conditions that decrease glomerular filtration rate or reduce proximal tubule secretion, such as renal disease, or the presence of inhibitors that compete for the transport system (e.g., probenecid). In case of an overdose, haemodialysis and hemofiltration techniques remove salicylic acid effectively from the circulation [1].

Monitoring of plasma salicylate concentrations

Aspirin is one of the NSAIDs for which plasma salicylate cam provide a means to monitor therapy and toxicity. Intermittent analgesic-antipyretic doses of aspirin typically produce plasma aspirin levels < 20 μg/ml and plasma salicylate levels < 60 μg/ml. The daily ingestion of anti-inflammatory doses of 4 to 5 grams of aspirin produces plasma acetylate levels in the range of 120 to 350 μg/ml. Optimal anti-inflammatory effects for patients with rheumatic diseases require plasma salicylate concentrations of 150 to 300 μg/ml. Significant adverse-effects can be seen at levels > 300 μg/ml. At lower concentrations the drug clearance is nearly constant (despite the fact that saturation of metabolic capacity is approached) because the fraction of drug that is free, and thus available for metabolism or excretion, increases as binding sites on plasma protein are saturated. The total concentration of salicylate is therefore relatively linear function of dose at lower concentration. At higher concentration, however, as metabolic pathways of disposition become saturated, small increments in dose can disproportionately increase plasma salicylate concentration. Failure to anticipate this phenomenon can lead to toxicity [1].

Therapeutic use of aspirin

The analgesic-antipyretic dose of aspirin is 325 to 1,000 mg orally 4 time-daily or 6 times-daily. It is only rarely used for inflammatory disease such as arthritis, spondyloarthropathies, and lupus erythematous; NSAIDs with better gastrointestinal safety profile are preferred. The anti-inflammatory doses of aspirin, as might be given in rheumatic fever; range from 4 to 8 grams daily in divided doses. The maximum recommended daily dose of aspirin for adults and children aged 12 years or older is 4 grams. The rectal administration of aspirin suppositories may be preferred in infants or when the oral route is unavailable. Aspirin suppresses clinical signs and improves tissue inflammation in acute rheumatic fever [1]. Aspirin is now seldom given to children because it is thought that use during viral illness can trigger Reye's syndrome (an acute life-threatening encephalopathy with fatty liver degeneration). It is still used in Kawasaki disease, in children with severe rheumatoid arthritis, and to limit coot formulation after cardiac surgery [2].



Molecular structure of aspirin (molecular weight = 180.158 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "aspirin dosing infants, children", "aspirin efficacy, safety infants, children", "aspirin effects infants, children", "aspirin metabolism", "aspirin pharmacokinetics infants, children", "aspirin treatment infants, children", "aspirin trials infants, children", "aspirin drug interactions", "aspirin human brain", "aspirin placental transfer", and "aspirin breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], and The British National Formulary for Children [3] have been consulted.

Results

Administration schedules of aspirin to infants and children

Administration to infants [2]

Kawasaki Disease: Give: 8 mg/kg (newborns) or 7.5 to 12.5 mg/kg (order infants) by mouth 4 times-daily for 2 weeks to control acute symptoms and then 5 mg/kg once-daily for 6 to 8 weeks. If there is no evidence of coronary lesions after sight weeks, it may be discontinued; if coronary artery lesions persist then the infant should remain on treatment.

Thrombus prophylaxis: A dose of 1 to 5 mg/kg is used for Fontan and Blalock-Tausig shunt surgery, and is also often given for 3 months after certain other forms of cardiac surgery to minimise the risk of clot formation until endothelial lining cells finally cover all postoperative scar tissue.

Administration to children [3]

Oral treatment of antiplatelet and prevention of thrombus formation after cardiac surgery

Children aged 1 month to 11 years. Give: 1 to 5 mg/kg once-daily (maximum per dose = 75 mg).

Children aged 12 to 17 years. Give: 75 mg once-daily.

Oral treatment of Kawasaki disease

Children aged 1 month to 11 years. Give initially 7.5 to 12.5 mg/kg 4 times-daily for 2 weeks until afebrile, and then 2 to 5 mg/kg once-daily for 6 to 8 weeks, if no evidence of coronary lesions after 8 weeks, discontinue the treatment or seek expert advice.

Efficacy and safety of aspirin in infants and children

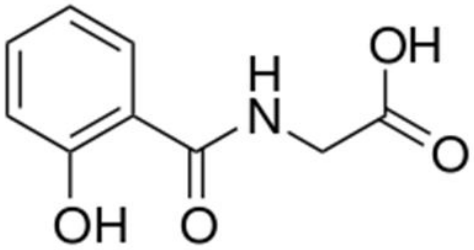
The daily use of low-dose aspirin (81 mg) is a safe intervention for reducing the risk of preterm birth [4]. Low-dose aspirin in women at risk of preeclampsia is associated with a reduced risk of preterm and neonatal outcomes [5]. Aspirin, given by mouth, is efficacy and safe in curing intestinal fluid loss in infants and young children with acute gastroenteritis [6]. Child-resistant packaging has been found effective in reducing aspirin-related child poisonings [7]. The safety packaging has reduced the incidence of aspirin ingestions from 45% to 55% in infants and in children the reduction ranges from 40% to 45% [8].

Effect of aspirin in infants and children

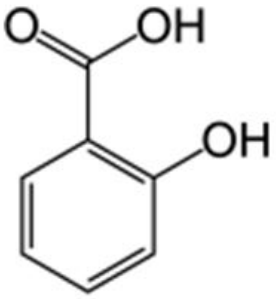
Aspirin treatment during pregnancy reduces the incidence of hemodynamically significant patent ductus arteriosus in preterm infant [9]. Aspirin is not as effective as indomethacin in closing the patent ductus arteriosus in preterm infants [10]. Low-dose of aspirin is associated with a reduction in neurobehavioral difficulties in infants [11]. Aspirin can normalize non-alcoholic fatty liver disease and atherosclerosis by inhibiting lipid biosynthesis and inflammation in children [12]. Aspirin reduces the inflammation of human skeletal muscle in children [13]. Aspirin plasma concentration should be monitored in order to optimize the therapy in children [14]. Aspirin releases eicosanoids and produces bronchospasm in children [15].

Metabolism of aspirin

The main metabolite of aspirin recovered in the urine is glycine conjugate and salicyluric acid which accounts for 75.01$\pm$1.19% of total urinary metabolites whereas salicylic acid accounts for 8.82$\pm$0.56%. Recovery of salicyluric acid was negatively correlated with that of salicylic acid ($r = -0.8625$, P-vale < 0.001). The plasma salicylate concentration ranges from 240 to 360 µg/ml, that of salicyluric acid accounts for 46.66$\pm$3.22% and that of salicylic acid is 31.88$\pm$4.02%. In 13 patients with plasma salicylate concentrations of 715 to 870 µg/ml, salicyluric acid accounts for 21.57$\pm$3.65% and salicylic acid accounts for 64.72$\pm$4.82% [16].

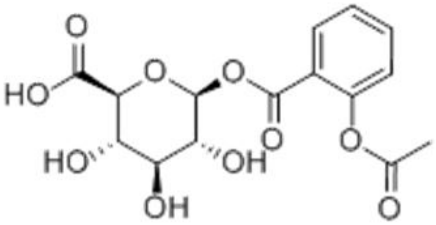


Salicyluric acid molecular structure (molecular weight = 195.174 grams/mole)

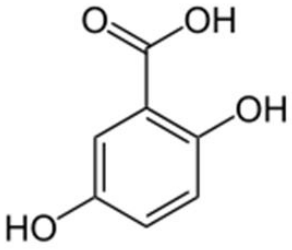


Salicylic acid molecular structure (molecular weight = 138.121 grams/mole)

In 129 volunteers treated with aspirin, the following products are identified in the urine: salicylic acid, its acyl and phenolic glucuronides, salicyluric acid, its phenolic glucuronide and gentisic acid. The excretion of salicylic acid is found to be highly variable within the study (1.3 to 31% of dose in 12 hours), and is related to both urine volume and pH. Salicyluric acid is the major metabolite excreted in the urine of volunteers and its excretion is normally distributed [17].

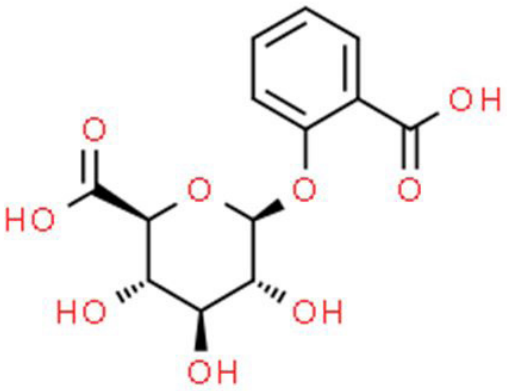


Aspirin-acyl-D-glucuronide molecular structure (molecular weight = 356.28 grams/mole)



Gentisic acid molecular structure (molecular weight = 154.12 grams/mole)

The major metabolites of salicylic acid are its acyl and phenolic glucuronide conjugates. The formation of these conjugates is catalysed by UDP-glucuronosyltransferases and this metabolism decreases the amount of pharmacologically active salicylic acid [18]. There are statistically significant differences in metabolites excreted by men and women. Men excreted more salicyluric acid and women excreted more aspirin (P-value = 0.03), salicylic acid, salicylic acid acyl glucuronide and salicylic acid phenolic glucuronide (P-value $\leq$ 0.001 for all) [19].



Salicylic acid acyl-β-D-glucuronide molecular structure (molecular weight = 314.24 grams/mole)

Pharmacokinetics of aspirin in children

Lares-Asseff et al. [20] studied the pharmacokinetics of aspirin and its metabolites in 11 underweight children and in 10 normal-weight children and aspirin was administered orally at a dose of 25 mg/kg 4 times-daily for 3 weeks. Table 1 reports the demographic characteristics of children and table 2 summarizes the pharmacokinetic parameters of aspirin, salicylic acid, gentisic acid, salicyluric acid.

Value	Age (month)	Actual weight (kg)	Median weight (kg)	Actual height (cm)	Median height (cm)
Underweight children (N = 11)					
Minimum	84	15.9	23.33	119	119
Maximum	180	46.4	58.19	160	166
Mean	142	32.2	42.25	140	147
SD	±8.8	±2.7	±4.59	±3.7	±4.3
Normal-weight children (N = 10)					
Minimum	31	13.2	14.56	88	95.1
Maximum	180	74.0	55.51	165	159
Mean	136	45.2	41.23	142	136
SD	±15.3	±6.3	±4.59	±8.7	±6.1
*P-value	0.7187	0.0837	0.8603	0.8294	0.1671

*Unpaired t test with Welch's correction.

Table 1: Demographic characteristics of children included in the study. Figures are the minimum, maximum, mean, and ±SD, by Lares-Asseff et al. [20].

This table shows that the demographic characteristics of underweight children are not statistically different from those of normal-weight children.

This table shows that the peak concentration of aspirin is greater in normal-weight than in underweight infants. The elimination-rate constant of aspirin is greater in underweight children, and that of salicylic acid, gentisic acid, and salicyluric acid is greater in normal-weight children. The total body clearance of aspirin is greater in normal-weight children. The AUC of aspirin is greater in normal-weight children and that of salicylic acid is greater in underweight than in normal-weight children. In conclusion, the metabolism of aspirin may vary in the two groups of children.

Value	Underweight children (N = 11)	Normal-weight children (N = 10)
Peak concentration (mmol/L)		
Aspirin	1.06 (0.12 – 1.66)	2.01 (0.46 – 54.07)[b]
Salicylic acid	124.7 (30.8 – 242.2)	49.35 (65.16 – 254.3)
Gentisic acid	3.98 (0.40 – 12.07)	3.91 (0.96 – 25.91)
Salicyluric acid	13.01 (0.46 – 31.60)	8.45 (0.84 – 50.38)
Elimination-rate constant (h^{-1})		
Aspirin	0.227 (0.142 – 0.276)	0.195 (0.065 – 8.855)[b]
Salicylic acid	0.206 (0.099 – 0.342)	0.294 (0.017 – 0.427)[b]
Gentisic acid	0.149 (0.035 – 0.624)	0.193 (0.039 – 0.939)[b]
Salicyluric acid	0.111 (0.061 – 0.343)	0.171 (0.008 – 1.970)[b]
Total body clearance (L*kg/h)		
Aspirin	0.280 (0.092 – 0.841)	0.842 (0.213 – 1.970)[b]
Salicylic acid	0.319 (0.052 – 0.813)	0.475 (0.039 – 1.073)
Gentisic acid	0.913 (0.037 – 1.172)	0.412 (0.057 – 2.400)
Salicyluric acid	0.473 (0.069 – 1.171)	0.210 (0.017 – 1.900)
AUC (mmol*h/L)		
Aspirin	14.51 (9.26 – 19.81)	28.95 (19.66 – 30.65)[b]
Salicylic acid	1,226 (889 – 1,343)	723 (478 – 983)[b]
Gentisic acid	42.19 (27.34 – 48.94)	48.93 (31.96 – 59.77)
Salicyluric acid	130.7 (89.72 – 220.8)	129.0 (91.85 – 164.5)

[a]Median (range). [b]Significantly different between underweight children and normal-weight children, P-value < 0.05 (Mann-Whitney U test).

Table 2: Pharmacokinetic parameters of aspirin, salicylic acid, gentisic acid, and salicyluric acid which are obtained in 11 underweight children and in 10 normal-weight children. Figures are the median and (range), by Lares-Asseff et al. [20][a].

Treatment of infants and children with aspirin

Pharmacokinetic considerations indicate that the aspirin dose should be corrected for individual size in order to optimize aspirin treatment and salicylate blood levels [21]. Salicylate toxicity should be considered in children with metabolic acidosis in order to prevent the severity of their illness [22]. The incidence of coronary artery aneurysm occurs with low-dose of aspirin compared to high aspirin dose [23]. Aspirin given at the dose of 20 to 29 mg/kg daily increases the risk of coronary damage compared to the dose of 30 to 50 mg/kg daily [24]. High-dose of aspirin has significant anti-inflammatory effect and does not produce adverse-effects in children [25]. Aspirin treats the acute-phase of Kawasaki disease in children [26]. Aspirin decreases the concentrations of tumour necrosis factor-α and increases C-reactive protein concentration [27]. Aspirin unresponsiveness is associated with increased risk of thrombosis after paediatric cardiac surgical procedures [28].

Trials conducted with aspirin in infants and children

Low-dose of heparin is not superior to aspirin in preventing recurrent stroke in paediatric patients [29]. Low-dose aspirin enhances the thrombotic risk in paediatric patients [30]. Naproxen is as effective and safer than aspirin in the treatment of rheumatic fever in children [31]. There is no difference in the efficacy and adverse-effects in patients treated with aspirin and naproxen [32]. Naproxen sodium provides earlier and better pain relief than aspirin and the incidence of adverse-effects associated with naproxen sodium is less than those caused by aspirin [33].

Interaction of aspirin with drugs

Aspirin competes with furosemide for a common secretory mechanism in the proximal tubule [34]. Morphine increases the total acetylsalicylic acid exposure by 20% compared with placebo when given simultaneously with aspirin [35]. Concomitant administration of nonsteroidal anti-inflammatory drugs with low-dose aspirin led to increased incidence of venous thromboembolism possibly

due to competitive inhibition of aspirin at platelet receptor sites [36]. Anti-inflammatory drugs offer effective pain and fever control and less serious adverse-effects than aspirin [37]. The prevalence of adverse gastrointestinal events is low when aspirin is co-administered with prednisolone [38]. Enalapril reduces the systemic vascular resistance more effectively when is given in combination with ticlopidine than with aspirin [39]. The combined use of sucralfate and aspirin is not likely to result in a clinically significant pharmacokinetic drug interaction [39].

Effects of aspirin on the human brain

Aspirin with corticosteroid adjunctive treatment is beneficial in reducing mortality in tuberculous meningitis [40]. Aspirin combined to antiangiogenic therapies shows synergetic anticancer efficacy in human primary glioblastoma-endothelial cells [41]. Patients on aspirin therapy have a markedly increased risk of subdural hematoma after a shunt has been implanted for the treatment of normal-pressure hydrocephalus [42]. Aspirin is a potential new therapy for a range of neuropsychiatric disorders [43]. Aspirin causes apoptosis via down-regulation of IL-6-dependent STAT3 signalling suggesting that aspirin could be therapeutically useful for anti-glioblastoma therapeutics [44]. Low-doses of aspirin are useful in the management of patients with cerebral ischemia, not only for its antithrombotic properties, but also by direct neuroprotective effects [45].

Transfer of aspirin across the human placenta

Concentrations of aspirin in maternal plasma, after 4 weeks of low-dose aspirin, are similar in umbilical cord plasma suggesting that aspirin rapidly crosses the placenta [46]. The transfer of aspirin was studied with the perfused human placental cotyledon and a rapid transfer of aspirin into the fetal-placental circulation is observed indicating that aspirin freely crosses the placenta [47].

Migration of aspirin into the breast-milk

Aspirin transfer into the breast-milk is so low that it is undetectable and salicylic acid does not appear in the breast-milk [48]. Following oral administration of 500, 1,000 and 1,500 mg aspirin to 6 healthy nursing mothers, aspirin appears in breast-milk, not later than one hour, and reaches its maximum levels (0.58, 1.60 and 3.87%, respectively, of the maternal plasma) [49]. A woman who was breastfeeding a 4-month-old infant was taking long-tern aspirin therapy in dosages ranging from 2 to 5.9 grams daily. The mean breast-milk aspirin level is 2 μg/ml and a peak level of 10 μg/ml occurs 3 hours after the dose. Aspirin levels ranges from 4 to 7 μg/ml over 5 hours after the peak [50].

Discussion

The effects of aspirin are largely caused by its capacity to acetylate proteins as described in irreversible cyclooxygenase inhibition by aspirin. Oral aspirin is rapidly absorbed, partially from the stomach, but mostly from the upper small intestine, and aspirin plasma concentration is reached in about 1 hour after dosing. The absorption-rate of aspirin is determined by disintegration and dissolution rates of the administered tablets, by the pH at the mucosa surface, and gastric empting time. Rectal adsorption of aspirin usually is slower than oral absorption and is incomplete and inconsistent and food delays the oral absorption-rate of aspirin. Aspirin distributes through most body tissues and transcellular fluids primarily by pH-dependent processes. In adults, the analgesic-antipyretic dose of aspirin is 325 to 1,000 mg orally 4- to 6-times-daily, and the anti-inflammatory doses of aspirin for the treatment of rheumatic fever is 4 to 8 grams daily [1]. In infants and children, aspirin is used to treat the Kawasaki disease and to prevent the thrombus formation. For the treatment of Kawasaki disease, the aspirin dose is 8 mg/kg in newborns and 7.5 to 12.5 mg/kg in older infants 4 times-daily and for the prophylaxis of thrombus formation the aspirin dose is 1 to 5 mg/kg once-daily [2]. In children, the oral aspirin dose is 7.5 to 12.5 mg/kg 4 times-daily to treat Kawasaki disease and 1 to 5 mg/kg once-daily for the prevention of thrombus formation and the aspirin dose varies according to the child age [3]. The aspirin efficacy and safety have been studied in infants and children [4-8]. A 81 mg daily dose of aspirin given to pregnant women reduces the risk of preterm birth [4], low-dose of aspirin administered to pregnant women reduces the risk of adverse neonatal outcomes [5], oral aspirin is efficacy and safe in curing intestinal fluid loss in infant with gastroenteritis [6], child-resistant packing has been found effective in reducing aspirin-related child poisoning [7], and the safety packing reduces the incidence of aspirin ingestions in about one half of infants and children [8]. The effects caused by aspirin have been described in infants and children [9-15]. Aspirin treatment during pregnancy reduces the incidence of patent

ductus arteriosus [9], but aspirin is not effective as indomethacin in closing the patent ductus arteriosus [10]. Low-dose of aspirin reduces the neurobehavioral difficulties in infants [11], aspirin normalizes non-alcoholic fatty liver disease and atherosclerosis by inhibiting lipid biosynthesis in children [12], aspirin reduces the inflammation of skeletal muscle in children [13], aspirin plasma concentration should be monitored in order to optimize the therapy in children [14], and aspirin releases eicosanoids and produces bronchospasm in children [15]. The metabolism of aspirin has been investigated [16-19]. The main metabolite recovered in the urine of volunteers is glycine conjugate and salicyluric acid which accounts for 75% of total metabolites whereas salicylic acid accounts for 8.8% [16], other metabolites are acyl and phenolic glucuronides and gentisic acid [17] and the major metabolites of salicylic acid are its acyl and phenolic glucuronide conjugates and these conjugates are catalysed by various UDP-glucuronosyltransferases [19]. The pharmacokinetics of aspirin and its metabolites have been investigated in normal-weight and underweight children. Following oral aspirin dosing, the elimination half-life of aspirin, salicylic acid, gentisic acid, and salicyluric acid is 0.195, 0.294, 0.193, and 0.171 hours, respectively, in normal-weight children but these half-lives vary in underweight children [20]. The treatment of infants and children with aspirin has been extensively studied [21-28]. Pharmacokinetic considerations indicate that aspirin dose should be corrected by the individual size [21], inappropriate use of aspirin may cause toxicity due to metabolic acidosis [22], the incidence of coronary artery aneurism occurs with aspirin low-dose compared to high dose [23], aspirin given at the dose of 20 to 29 mg/kg daily increases the risk of coronary damage compared to the dose of 30 to 50 mg/kg daily [24], high-dose of aspirin has significant anti-inflammatory effect and does not produce adverse-effects in children [25], aspirin treats acute Kawasaki disease in children [26], and aspirin decreases the concentrations of tumour necrosis factor-α and increases C-reactive protein concentrations [27], aspirin unresponsiveness is associated with increased risk of thrombosis after a paediatric cardiac surgical procedures [28]. The trials have been conducted in infants and children [29-33]. Low-dose of heparin is not superior to aspirin to treat stroke in paediatric patients [29], low-dose aspirin enhances the thrombosis risk in paediatric patients [30], naproxen is effective and safe as aspirin in the treatment of rheumatic fever in children [31, 32], and naproxen provides earlier and better pain relief than aspirin [33]. Aspirin interacts with drugs [34-39]. Aspirin competes with furosemide for a common secretory mechanism in proximal tubule [34], morphine increases the acetylsalicylic exposure when is co-administered with aspirin [35], concomitant administration of nonsteroidal anti-inflammatory drugs with low-dose of aspirin increases the incidence of venous thromboembolism [36], anti-inflammatory drugs control pain and fever and induce less adverse-effects than aspirin [37], the combination of prednisolone with aspirin yields lower adverse gastrointestinal events [38], the co-administration of enalapril and ticlopidine reduces the vascular resistance better than the combination of enalapril with aspirin [39], and the combined use of sucralfate and aspirin does not cause significant pharmacokinetics interaction [39]. Aspirin causes different effects on the human brain [40-45]. Aspirin co-administered with corticosteroids reduces the mortality in tuberculous meningitis [40], the combination of antiangiogenic therapies with aspirin has synergistic activity in human glioblastoma-endothelial cells [41], aspirin increases the risk of subdural hematoma in patients who had an implantation to treat hydrocephalus [42], aspirin is a potential therapy for a range of neuropsychiatric disorders [43], aspirin causes apoptosis by down-regulation of IL-6-dependent STAT3 signalling and is a useful tool for anti-glioblastoma therapeutics [44], and low-doses of aspirin are useful in the management of cerebral ischemia [45]. The transfer of aspirin across the human placenta has been studied in-vivo [46] and in-vitro using the placental perfusion [47] and aspirin freely crosses the human placenta. The migration of aspirin into the breast-milk has been studied in three occasions and aspirin poorly migrates into the breast-milk [48-50].

In conclusion, the effects of aspirin are largely caused by its capacity to acetylate proteins as described in irreversible cyclooxygenase inhibition by aspirin. Aspirin may be administered intravenously, orally, or rectally and following oral administration aspirin is rapidly absorbed whereas after rectal administration the absorption is incomplete and inconsistent. Aspirin is used to treat the Kawasaki disease and to prevent of thrombus formation in infants and children. For the treatment of Kawasaki disease the oral dose is 8 mg/kg in newborns and 7.5 to 12.5 mg/kg in older children 4 times-daily and for the prevention of thrombus formation the dose is 1 to 5 mg/kg once-daily. In children, the Kawasaki disease is treated with 7.5 to 12.5 mg/kg 4 times-daily and for the prevention of thrombus formation the aspirin oral dose is 1 to 5 mg/kg once-daily, and the aspirin dose varies according to the child age. Aspirin has been found efficacy and safe in infants and children and aspirin effects have been studied in infants and children. Aspirin is extensively metabolized; the metabolites are salicylic acid, gentisic acid, and salicyluric acid and aspirin and salicylic acid are glucuronidated. The pharmacokinetics of aspirin, salicylic acid, gentisic acid and salicyluric acid have been studied in children. The treatment and trials with aspirin have been studied in infants and children, aspirin interacts with drugs, and aspirin causes different effects on the human brain. Aspirin freely crosses the human placenta and poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of aspirin 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.

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