Introduction

Fever and pain are common in children, especially as a result of infections, such as otitis media (1). In paediatric populations, the over-the-counter (OTC) medicines ibuprofen and paracetamol (acetaminophen) are both commonly used for the management of fever or mild-to-moderate pain associated with sore throat, otitis media, toothache, earache and headache. Children are most likely to experience acute pain as a result of illness, injury or medical procedures. Fever in a child is one of the most common clinical symptoms managed by paediatricians and other healthcare providers and accounts for at least one third of all presenting conditions in children (2).

Widespread use of ibuprofen and paracetamol has shown that they are both effective and generally well tolerated in the reduction in paediatric fever and pain although, surprisingly, optimal doses, dosing regimens and choice of medication are not clearly described in the scientific literature (3,4). Despite the extensive use of ibuprofen and paracetamol, adverse events (AEs) with the therapeutic use of these drugs seem to be uncommon.

Ibuprofen is better tolerated than other non-steroidal anti-inflammatory drugs (NSAIDs), although it
Physiology of fever

It is important to emphasise that fever is not an illness, but a physiological mechanism that has beneficial effects in fighting infection. Fever slows the growth and replication of bacteria and viruses, enhances neutrophil production and T-lymphocyte proliferation and aids in the body’s acute-phase reaction (18). The degree of fever does not always correlate with the severity of illness. Most fevers are of short duration, are benign, and may actually protect the host (19). There are data showing beneficial effects on the immune system and even some data indicating that fever may actually help the body to recover more rapidly from viral infections, although the fever may result in discomfort in children (20). There is no evidence that children with fever are at an increased risk of adverse outcomes (21).

Pathophysiology of fever

Body temperature is regulated by the preoptic anterior hypothalamus. Under normal circumstances, this thermoregulatory centre maintains body temperature in a narrow physiological range by balancing the heat produced by muscle and liver metabolism with the amount of heat primarily lost through the skin and lungs.

Fever, a cytokine-mediated increase in core body temperature, is one component of the febrile response, a physiological reaction to disease that involves activation of various physiological, endocrinological and immunological systems (22). Although primarily a reaction to infection, the febrile response is also seen in other inflammatory and immunological diseases including malignancy and autoimmune disease.

Fever is initiated by the pyrogenic cytokines, namely interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma). Cytokines are nonstructural proteins produced in response to cell stress. Almost all nucleated cells are capable of producing and responding to cytokines. Cytokines remain undetectable in the serum of normal subjects under basal conditions. IL-1, IL-6, TNF-alpha and IFN-gamma are intrinsically pyrogenic in that they rapidly induce fever by acting on the hypothalamic thermoregulatory centre.

The fever pathway is initiated when exogenous pyrogens, such as microbes and/or their toxins (e.g. lipopolysaccharide or LPS), enter the body through a defect in host barriers, stimulating mononuclear phagocytes to release the aforementioned pyrogenic cytokines. These cytokines travel in the systemic circulation to the organum vasculosum laminae terminalis (OVLT), a rich vascular network abutting the hypothalamus with a minimal blood–brain barrier. The importance of the OVLT has been demonstrated in studies showing that fever does not ensue after peripheral administration of pyrogenic cytokines to

Hepatotoxicity appears to be the most serious and well-documented AE associated with paracetamol use in children. Case reports have suggested that liver failure can occur with chronic treatment with doses just above the recommended maximum dose (10). Urticaria and maculopapular rashes have been attributed to paracetamol use (11). Recently, a strong epidemiological association between paracetamol use and asthma has emerged in the literature (12). This epidemiological association of asthma and paracetamol has been confirmed in two publications from Phase III of the International Study of Allergy and Asthma in Childhood (13,14). That study included data on 200,000 children aged 6–7 years and 320,000 children aged 13–14 years from more than 40 countries. In both age groups, there was a paracetamol dose-dependent increase in the prevalence and severity of asthma. Children who took paracetamol at least monthly were more than three times as likely to report asthma at 6–7 years of age and more than twice as likely at ages 12–14 years.

Unfortunately, as many as one half of parents administer incorrect doses of either paracetamol or ibuprofen, and approximately 15% of parents give supratherapeutic doses of both these OTC medicines (15). Clearly, antipyretic and analgesic therapy will remain a common practice by parents and it is generally encouraged and supported by paediatricians.

From a practical standpoint the World Health Organization (WHO) recommended dose of ibuprofen is 5–10 mg/kg orally every 6–8 h, to a maximum of 500 mg/day (16). For paracetamol, the WHO recommended dose is 10–15 mg/kg every 4 h. Aspirin is not recommended in children who are 16 years of age or less owing to its implication in the development of Reye’s syndrome (17).

This review will summarise the physiology of fever, the pathophysiology of fever, antipyretic therapy, and clinical pharmacology aspects of using medicines in children.
rats with ablated OVLTs. However, when these same cytokines are injected directly into the brain, ablation of the OVLT does not prevent fever (23). Thus, it seems that the OVLT is the gateway between the peripheral systemic circulation and the protected circulation within the brain itself.

The exact mechanism of interaction between the pyrogenic cytokines and the OVLT remains unknown. It is postulated that the pyrogenic cytokines trigger the arachidonic acid cascade in the endothelial cells of the OVLT and that prostaglandin E_2 (PGE_2), an end product of the cascade, then induces cyclic adenosine monophosphate (cAMP) to act on the thermoregulatory nuclei of the hypothalamus, causing an elevation in the thermal set point (24).

With the set point as a reference, the hypothalamus then perceives the current body temperature as inadequate and coordinates an elevation of temperature. This is accomplished by accelerated heat production (shivering, increased muscle tone, increased metabolism, etc.), restricted heat loss (cutaneous vasoconstriction and cessation of sweating) and heat-seeking behaviours (25).

**Antipyretic therapy: mechanism of action**

To understand the mechanisms of action of the antipyretic agents considered herein, it is necessary to review the components of the arachidonic acid cascade. Following proper stimulation (e.g. by an exogenous pyrogen), the cascade begins with the release of phospholipids from cell membranes. Once liberated, the phospholipids are converted to arachidonic acid by phospholipase A₂. Arachidonic acid is then converted to prostaglandin by cyclooxygenase-2 (COX-2). Prostaglandin synthetase acts on the prostaglandin to produce PGE₂, a proinflammatory mediator causing pain, fever, erythema and oedema.

It is important to note that arachidonic acid is a substrate for both COX-2 and a second isofrom of the enzyme, COX-1. Although COX-2 is an inducible form of the enzyme not normally detectable in cells, COX-1 is constitutively expressed. COX-2 is the principal mediator of the inflammatory response, thus resulting ultimately in production of PGE₂, COX-1 products, on the other hand, function primarily in renal function, vascular homeostasis and gastrointestinal cytoprotection.

**Paracetamol**

The mechanism of action of paracetamol is not entirely understood, but it is thought that it acts centrally to convert the active oxidised form of COX to the inactive reduced form and that this central inhibition of COX is responsible for the antipyretic effects of paracetamol. As paracetamol does not inhibit COX in peripheral tissues, it lacks anti-inflammatory activity and is, therefore, not an NSAID. Paracetamol also lacks effect on peripheral COX-1 functions, including renal function, vascular homeostasis and gastrointestinal cytoprotection. Paracetamol doses of 10–15 mg/kg per dose given every 4–6 h orally are generally regarded as well tolerated and effective. Typically, the onset of an antipyretic effect is within 30–60 min. Approximately 80% of children will experience a decreased temperature within that time span. There is no consistent evidence that the use of an initial loading dose by either the oral (30 mg/kg per dose) or rectal (40 mg/kg per dose) route improves antipyretic efficacy. The use of higher loading doses in clinical practice would add potential risks for dosing confusion leading to hepatotoxicity. Therefore, such doses are not recommended (26).

**Ibuprofen**

Ibuprofen is a competitive inhibitor of the COX enzymes in that it competes with arachidonic acid for binding to the catalytic site on COX, thereby preventing prostaglandin synthesis. This competitive binding is reversible. Unlike paracetamol, ibuprofen acts peripherally. Furthermore, ibuprofen lacks specificity for either COX isomer. For these reasons, ibuprofen inhibits COX-2, reducing fever and inflammation, thus making it a non-steroidal anti-inflammatory agent or NSAID. However, ibuprofen also has side effects associated with its inhibition of COX-1, including gastrointestinal upset. Concern has been raised over the nephrotoxicity of ibuprofen. In numerous case reports, children with febrile illnesses developed renal insufficiency when treated with ibuprofen or other NSAIDs. Thus, caution is encouraged when using ibuprofen in children with dehydration (27). However, there are not enough data to support a specific recommendation for the use of ibuprofen for fever or pain in young infants (< 6 months of age). The use of ibuprofen to manage fever has been increasing because it seems to have a longer clinical effect related to the lowering of body temperature.

**Paracetamol vs. ibuprofen**

Studies in which the effectiveness of ibuprofen and paracetamol were compared have shown variable results. However, the consensus is that both drugs are more effective than placebo in reducing fever and that ibuprofen (10 mg/kg per dose) is as least as
effective as, and perhaps more effective than, paracetamol (15 mg/kg per dose) in lowering body temperature when either drug is given as a single or repetitive dose (28,29).

However, another study concluded that to maximise the time that children spend without fever, one should use ibuprofen first and consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 h (30). Overall, there is no evidence to indicate that there is a significant difference in the safety of standard doses of ibuprofen vs. paracetamol in generally healthy children between 6 months and 12 years of age with febrile illnesses (31).

**Clinical pharmacology aspects**

Children younger than 15 years old account for 28% of the population worldwide. As one must undergo the developmental trajectory of childhood to reach adulthood, any discussion of optimising the management of fever and pain in children would be incomplete without inclusion of how development, the most dynamic period of human life, influences drug disposition and action and creates unique therapeutic scenarios that are not seen in adults.

Despite being a continuum of physiological events that culminate in maturity, development is often arbitrarily divided into the stages of infancy, childhood, adolescence and even early adulthood. Across this period of time organ size and function change as does body composition, protein expression and cellular function. Some tissues may be more sensitive to pharmacological effects early in life, whereas later in life function may decline. As these developmental changes in function and form occur, their implications with respect to the clinical pharmacology of drugs and their appropriate place in paediatric therapy must be considered.

**Developmental clinical pharmacology**

Throughout development, the impact of ontogeny on pharmacokinetics and pharmacodynamics is, to a great degree, predictable and follows definable physiological ‘patterns’. This study will only focus on developmental changes in metabolism and elimination of drugs and, more specifically, issues relevant to the metabolism and elimination of ibuprofen and paracetamol.

**Ontogeny of drug metabolism in children**

The cytochrome P450 family of enzymes is responsible for the biotransformation of both endogenous substrates and therapeutic agents used, such as paracetamol and ibuprofen in infants, children and adolescents. There are considerable differences in the expression and activity of these enzymes along the developmental spectrum. At birth, the total hepatic cytochrome P450 concentration is approximately 30% of adults and there are variable rates of maturation both quantitatively and functionally (32,33). CYP2C9 is a polymorphically expressed enzyme, which catalyses the biotransformation of several important drugs used in paediatrics (e.g. phenytoin, ibuprofen, indomethacin). CYP2C9 has been detected at very low levels (1% of adult levels) in early gestation (earliest at 8 weeks). At full term, activity increases to approximately 10% of that observed in adults and by 5–6 months of age, is approximately 25% of adult levels. A similar pattern of developmental expression is demonstrated for CYP2C19, an enzyme which is also polymorphically expressed and largely responsible for the biotransformation of proton pump inhibitors (e.g. lansoprazole, omeprazole, pantoprazole, esomeprazole, rabeprazole); a drug class used extensively in neonates and infants with gastro-oesophageal reflux. CYP2C19 activity increases quickly after birth and reaches adult levels at approximately 6 months of postnatal age (34). It is at this point (which is the same for CYP2C9) that genotype–phenotype concordance is expected and predictive relationships between the CYP2C19 genotype and the activity of the enzyme are apparent. In examining the ontogeny of both CYP2C9 and CYP2C19 (as is the case with most all of the cytochrome P450 isoforms), significant inter-subject variability is apparent across the developmental continuum. Also, when constitutive activity of the enzyme is normally low shortly after birth, genotype–phenotype discordance is evident and thus genotypic classification of metaboliser status can be errant.

Of the cytochrome P450 isoforms quantitatively important for drug metabolism in humans, all studies to date appear to have a developmental pattern with respect to the attainment of activity. However, it is beyond the scope of this review to provide a detailed description for each enzyme, as this has already been accomplished in recent reviews on the topic (35).

In overdose, paracetamol produces a centrilobular hepatic necrosis that can be fatal. The importance of metabolism in paracetamol toxicity has been established. Paracetamol is metabolically activated by cytochrome P450 isoforms CYP2E1, CYP1A2, CYP3A4 and CYP2A6 (36–38) to form a reactive metabolite, N-acetyl-p-benzoquinone imine that covalently binds to protein, causing toxicity. At therapeutic doses, the
reactive metabolite is quickly detoxified by combining irreversibly with the sulphhydryl group of glutathione to produce a non-toxic conjugate that is eventually excreted by the kidneys (39).

In addition to the development of the cytochrome P450 family of enzymes (Phase I), knowledge regarding the ontogeny of Phase II drug metabolising enzymes UDP-glucuronosyltransferases (UGT) is of great importance when prescribing drugs, such as chloramphenicol, morphine, paracetamol and zidovudine. These drugs are all UGT substrates that will have a requirement for alteration of dosing regimen to compensate for reduced enzyme activity in the first weeks and months of life. In premature infants (gestational age 24–37 weeks), the plasma clearance of morphine was found to be five-fold lower relative to older children. The clearance of morphine, a predominant UGT2B7 and UGT1A1 substrate, generally reaches adult levels between 2 and 6 months of age. However, considerable variability exists (40).

Paracetamol glucuronidation (a substrate for UGT1A6 and UGT1A9) is present in the fetus and newborn at very low levels (1–10% of adults). Following birth, activity steadily increases with levels approaching (~50%) by 6 months of age and full maturation by puberty. A similar profile is seen for zidovudine, a substrate for UGT2B7. Zidovudine clearance is significantly reduced in children < 2 years of age relative to older children, which also leads to a developmental difference in haematological toxicity (anaemia) caused by this drug (41).

Similar to what is seen for the UGT isoforms, ontogenic profiles also exist for glutathione s-transferase (GST), N-acetyltransferase (NAT), epoxide hydrolase (EPHX) and the sulfotransferases (SULT), but this is clearly beyond the scope of this review.

**Elimination**

Drug elimination in paediatric patients can occur via multiple routes, which include exhalation, biliary secretion and renal clearance. Of these, the kidney is quantitatively the most important. The kidney is the primary organ responsible for the excretion of drugs and their metabolites. The development of renal function begins during early fetal development and is complete by early childhood. From a developmental perspective, renal function is highly dependent on gestational age and postnatal adaptations. Renal function begins to mature early during fetal organogenesis and is complete by early childhood. Increases in glomerular filtration rate (GFR) result from both nephrogenesis, a process that is completed by 34 weeks of gestation, and changes in renal and intrarenal blood flow. GFRs vary widely among different postconceptional ages and range from approximately 2–4 ml/min/1.73 m\(^2\) in full-term neonates to a low of 0.6–0.8 ml/min/1.73 m\(^2\) in preterm neonates. The GFR increases rapidly during the first 2 weeks of life and then more slowly until adult values are reached by 8–12 months of postnatal age (42,43). Development impacts not only GFR, but also tubular secretion, which is immature at birth and reaches adult capacity during the first year of life.

Developmental changes that occur in renal function are better characterised than any other organ system. For drugs that have substantial renal clearance, kidney function serves as a major determinant of age-specific drug dosing regimens. Failure to account for the ontogeny of renal function and adjust dosing regimens accordingly can result in a degree of systemic exposure that can increase the risk of drug-associated AEs. It is also important to note that use of some medications concomitantly (i.e. betamethasone, ibuprofen and indomethacin) may cause alteration of the normal pattern of renal maturation in the neonate (44). Therefore, both maturation and effects of treatment with regard to renal function are important considerations when determining appropriate drug treatments in young infants.

As denoted above, development produces profound differences in processes that, collectively, can influence all facets of drug disposition (i.e. absorption, distribution, metabolism and excretion). Knowledge of the impact of ontogeny on the physiological determinants of drug disposition enables prediction of how development per se can impact pharmacokinetics and also, enables the clinician to use this information as a tool for designing age appropriate drug regimens. A recent review by van den Anker et al. describes the implications of developmental pharmacokinetics on paediatric therapeutics (45).

**Conclusion**

Ibuprofen is an effective analgesic and antipyretic drug for the treatment of childhood pain and fever. Ibuprofen has the advantage of less frequent dosing (every 6–8 h vs. every 4 h for paracetamol) and its longer duration of action makes it a suitable alternative to paracetamol. In comparative trials, ibuprofen has been shown to be at least as effective as paracetamol as an analgesic and more effective as an antipyretic (46,47). The safety profile of ibuprofen is comparable with that of paracetamol. However, there is a need for additional studies to investigate the safety of these medications in different paediatric
populations and determine the effects over prolonged use. Most importantly, the recently reported association between frequency and severity of asthma and paracetamol use needs urgent additional investigations (12).

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Author’s contribution

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