REVIEW

Paracetamol: a focus for the general pediatrician

Pierluigi Marzuillo · Stefano Guarino · Egidio Barbi

Abstract Paracetamol (acetaminophen) is one of the most popular and widely used drugs for the treatment of pain and fever in children. This drug has multiple mechanisms of action, but its pharmacodynamic is still not well known. The central nervous system is the main site of action and it mirrors the paracetamol effect compartment. The recommended dosages and routes of administration should be different whether paracetamol is used for the treatment of pain or fever. For example, the rectal route, while being efficacious for the treatment of fever, should be avoided in pain management. Paracetamol is a safe drug, but some clinical conditions and concomitant drugs, which are frequent in clinical practice, may increase the risk of paracetamol toxicity. Therefore, it is important to optimize its administration to avoid overdoses and maximize its effect. The principal mediator of the paracetamol toxicity is the N-acetyl-p-benzo-quinone imine (NAPQI), a toxic product of the paracetamol metabolism, which could bind cysteine groups on proteins forming paracetamol–protein adduct in the liver. *Conclusion*: Although frequently prescribed, the concept of "effect compartment concentration" and the possible co-factors that could cause toxicity at recommended doses are not familiar to all pediatricians and general practitioners. We reviewed the literature concerning paracetamol mechanisms of action, we highlighted some relevant pharmacodynamic concepts for clinical practice, and we summarized the possible risk factors for toxicity at therapeutic dosages.

P. Marzuillo (✉) · S. Guarino
Department of Women and Children and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Via L. De Crecchio 2, 80138 Naples, Italy
e-mail: pierluigi.marzuillo@gmail.com

E. Barbi
Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy

Introduction

Paracetamol (acetaminophen) is the most popular analgesic and antipyretic drug for the treatment of pain and fever in children. It represents the drug of choice for the management of mild to moderate pain and, according to NICE guidelines, for the management of the children with fever who appear distressed [112].

Increased paracetamol prescription followed an association noted between Reye's syndrome and aspirin [29].

The mechanisms by which paracetamol achieves its effects on pain are still debated. Paracetamol is generally considered to be safe and effective in recommended doses, even if concerns have arisen over the past decade as paracetamol has been increasingly recognized as a major cause of acute liver failure in adults in the United States [62].

While paracetamol is an important cause of acute liver failure in children, it plays a relatively small role in the etiology of acute liver failure from a global standpoint [107]. A recent report showed that a significant number of adults develop elevations in hepatic transaminase levels while receiving recommended doses of paracetamol in a controlled research setting [117].

Elements of pharmacokinetics: how is paracetamol absorbed and metabolized?

Absorption

Paracetamol has a pK_a of 9.5, and, in the alkaline medium of duodenum, is largely non-ionised and consequently absorbed

primarily by passive non-ionic diffusion [13]. Absorption within the stomach is minimal, and the limiting step for absorption is gastric empting into the duodenum [40]. Absorption may be altered by formulation. Bioavailability for the oral route is estimated at 63–89 % [16, 105]. Tablets and capsules must disintegrate and then dissolute, introducing a lag time before duodenal uptake. Paracetamol effervescent tablets [100] and liquid paracetamol (elixir, drops, syrup) [16] are absorbed significantly faster. The time to peak concentration is approximately 45 to 60 min after oral administration of regular release tablets and there may be large variation in individual plasma paracetamol concentrations measured 60 min after oral administration [16]. Liquid paracetamol has a time to peak of about 30 min [16].

The absorption from the rectal route is considered the most erratic and unpredictable, with reported values of bioavailability ranging from 24 % to 98 % [32, 105]. For the rectal route, the time to peak plasma concentration ranges from 107 to 288 min after rectal administration [32].

Age also has an impact on paracetamol absorption. Because of slower gastric empting, oral absorption in neonates is delayed [5]. Normal adult rates may not be reached until 6–8 months of age [41].

The IV route of administration shows consistently earlier and higher peak plasma or cerebrospinal fluid (CSF) concentration than oral or rectal routes [105].

Distribution

The binding of paracetamol to plasma proteins is low (10–25 %) [28], while it is widely distributed, with a volume of distribution of 0.8–1 l/kg [95].

Because of differences in body composition (e.g., higher body water content) and because of the fact that paracetamol is a water-soluble compound, the distribution volume is higher in the newborn: the peripheral volume of distribution decreases from 27 weeks postmenstrual age (45.0 1×70 kg^{-1}) to reach 110 % of its mature value by 6 months of age [10]. Paracetamol has been shown to be able to penetrate into the CSF. It is also able to penetrate in the placenta and is excreted in breast milk at low levels [14, 15, 61]. The estimated maximum dose to the neonate through breast milk was 1.85 % of the weight-adjusted maternal oral dose of paracetamol (1.0 g) [80].

The concept of effect compartment concentration

Time delays between paracetamol concentrations and analgesic effect have been reported in adult volunteers [12, 79] and children [11]. Moreover, several studies have documented a time delay of 1–2 h between maximum plasma concentration and maximum temperature reduction (Fig. 1) [40, 54, 119].

These time delays mean that there is not a direct relationship between concentration and effect. Paracetamol must
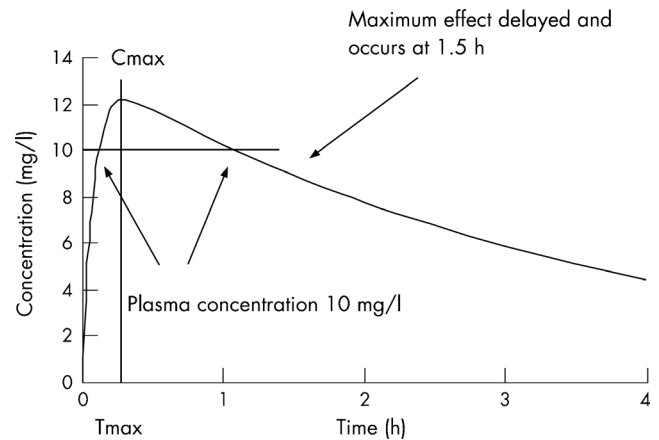

Fig. 1 Time–concentration profile for a child given paracetamol elixir. A concentration of 10 mg/l is reached both before (during the absorption phase) and after (elimination phase) maximum concentration. There is a delay between maximum concentration and peak effect of about 1 h. (Data from Gibb and Anderson [40])

move from the plasma to an effect compartment where exerts its pharmacological action [40] and the CSF compartment mirrors the paracetamol effect compartment.

There is an important difference in the required effect compartment concentrations for analgesia and fever reduction. A minimum target effect compartment concentration of 10 mg/l is required for pain relief in children (Fig. 2) [11] and recently confirmed also in neonates [4]. The minimum target effect compartment concentration for antipyresis is 5 mg/l (Fig. 3) [40]. The effect compartment concentration of 10 mg/l is obtainable both with i.v. [10] and oral routes [40]; at standard doses, the rectal route can provide an effect compartment concentration of 5 mg/l [40]. To obtain a higher effect, compartment concentration with rectal route should require much higher and not safe doses.
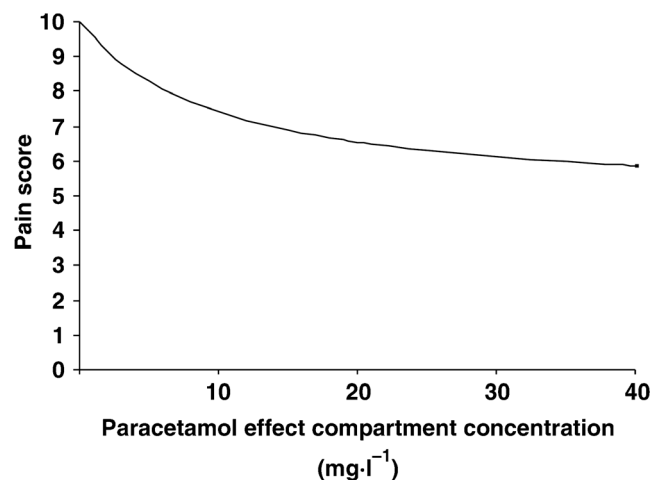
Fig. 2 Effect compartment concentration–analgesic response relationship for paracetamol in children after tonsillectomy. Small concentration increases have maximal effect up to effect compartment concentration of 10 mg/l. Further increasing concentration has minimal effect on pain score. A VAS pain score (0–10) measured effectiveness. (Data from Anderson et al. [11])
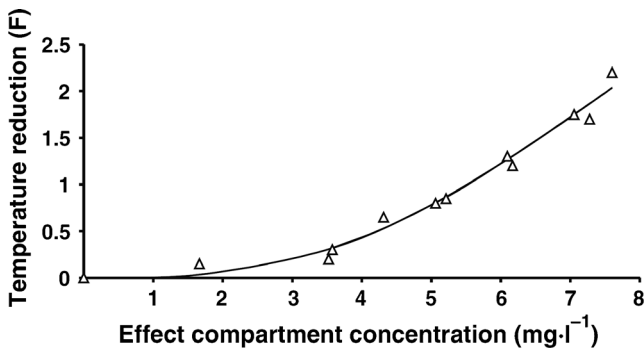
Fig. 3 Effect compartment concentration–response relationship for paracetamol antipyresis. The temperature reduction is expressed in Fahrenheit (F). (From Anderson [8])

The clinical relevance of these concepts is that the needed outcome (analgesia or antipyresis) must drive the route of administration (e.g., rectal route is not appropriate for pain management). The choice of the interval of the drug administration could be also driven by the evidence of the time delay between maximum plasma concentration and maximum effect [40]. Therefore, if needed, the anticipation of the dose administration can allow an efficacious and steady concentration in the effect compartment, with a minimum interval of administration of 4 h.

Metabolism and elimination

In adults, paracetamol is metabolized mainly in the liver by glucuronidation (50–60 %), sulfation (25–30 %), and oxidation (<10 %) [84, 93]. Additionally, hydroxylation to form 3-hydroxyparacetamol and methoxylation to form 3-methoxyparacetamol, along with excretion of free or unconjugated paracetamol in the urine, represent minor clearance pathways [73]. Paracetamol is subject to a first pass hepatic metabolism, which justifies the variability of absorption between patients [16] and between different ages [5].

None of the metabolites of paracetamol has analgesic or antipyretic effects. All of the metabolites are excreted in the urine in a dose-dependent manner, with more than 90 % of an administered dose excreted within 24 h. Enterohepatic circulation is negligible [53]. The renal elimination capacity is reflected by diuresis, glomerular filtration rate and renal tubular activity. The extensive variability in early infancy relates to maturation (e.g., age, birthweight) and disease characteristics (e.g., peripartal asphyxia, renal congenital malformations) [5].

Oxidation of paracetamol occurs via a CYP450-dependent, mixed-function oxidase enzyme pathway, primarily by CYP2E1 and CYP3A4, to form *N*-acetyl-*p*-benzo-quinone imine (NAPQI) [66]. NAPQI is near-instantaneously conjugated with intracellular glutathione to 3-glutathione-*S*-yl-paracetamol by reacting with either intracellular glutathione directly or through a glutathione-transferase-catalyzed reaction [33]. NAPQI may cause hepatotoxicity after a massive acute overdose if glutathione stores are exhausted. With therapeutic doses of paracetamol, sufficient glutathione stores are present to conjugate the small amount of NAPQI produced. Additionally, there is an active repletion process for glutathione [63].

In children, paracetamol metabolism pathways are the same as in adults, but the relative contribution of each pathway or enzyme to the overall paracetamol metabolism changes with age.

The sulfation pathway is mature at birth; however, the glucuronidation pathway takes about 2 years to mature [114]. As the glucuronidation activity in younger children is less than that seen in older children and adults, the sulfation pathway is a more important route of metabolism for paracetamol in younger children [72]. Even if the rate of excretion of various paracetamol metabolites changes with age, the plasma half-life of paracetamol is similar across different age groups [72].

CYP2E1 levels are low in neonates, and gradually increase during the first year to reach the adult value in children aged 1–10 years [115].

However, in neonates, metabolic clearance of paracetamol through sulfation matures more rapidly than glucuronidation which is still poor. This results in lower clearance and slower decrease after the peak paracetamol concentration has been reached. Because of this lower clearance, accumulation is more likely [5].

The development of hepatotoxicity caused by paracetamol is dependent on the balance of the formation rate of NAPQI, the elimination rate from sulfation and glucuronidation conjugation pathways, and the initial content and repletion rate of hepatic glutathione [83].

Young children appear to be most resistant to paracetamol-induced hepatotoxicity because of both reduced rates of oxidation by CYP2E1 and the neonate's increased ability to replete glutathione compared with adults [91].

Elements of pharmacodynamics: how does paracetamol act?

It has been assumed that paracetamol mainly acts through the cyclooxygenase (COX) pathway. Its action appears to be mostly central; it readily passes the blood–brain barrier [30, 61] and inhibits prostaglandin synthesis in the brain [9, 39]. The inhibition of the prostaglandin synthesis in the brain leads to temperature reduction probably modifying hypothalamic temperature set-point [39].

Paracetamol does not have significant anti-inflammatory activity nor does inhibit production of the pro-clotting trombaxane 2 (TXA2). Paracetamol does not appear to have a major effect peripherally, which explains both its favorable lack of several adverse effects associated with NSAIDs, such as stomach ulcers, impaired hemostasis, reduced renal flow

and the absence of anti-inflammatory (positive) effects in the settings of inflammation (e.g., arthritis).

The mechanism of action of paracetamol analgesia is multifactorial. Inhibition of prostaglandin synthesis in the brain plays a major role, but alternative mechanisms of action are proposed:

- Central serotonergic mechanism: paracetamol could activate the serotonergic inhibitory descending pain pathways with analgesic effect [90].
- Effect on cannabinoid (CB) receptors: two research groups [48, 82] have demonstrated an active metabolite of paracetamol (the fatty acid amide N-arachidonoylphenolamine) that shares the ability of CBs to display analgesic activity and to lower body temperature [19, 42].
- Inhibitory action on spinal L-arginine–nitric oxide (NO) pathway: depolarization of afferent neurons by peripheral harmful stimuli leads to activation of spinal N-methyl-D-aspartate (NMDA) receptors. Rodent studies suggest that these, in turn, promote the synthesis of NO (a neurotransmitter at a spinal level conveying nociceptive information) [49, 70]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol interfere with nociception associated with spinal NMDA receptor activation. This effect may involve an inhibitory action on spinal NO mechanisms [20].

Elements of pharmacodynamics: side effects

Paracetamol is usually well tolerated at recommended therapeutic doses. Rash and other allergic reactions occur occasionally. The rash usually is erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions [58]. The use of paracetamol has been associated anecdotally with neutropenia, thrombocytopenia, and pancytopenia [37, 121]. Hypotension, flushing, and tachycardia are also reported on infusion [21].

Several observational studies have reported associations between paracetamol use in children and asthma, some epidemiological evidence links paracetamol exposure in pregnancy and childhood with asthma [45]. The underlying biological mechanisms are not clear. The paracetamol use might influence asthma pathogenesis through depletion of glutathione, a major antioxidant in the airways [104]. This might influence asthma in two ways. The toxic metabolite NAPQI may increase oxidative stress causing epithelial damage and increased airway inflammation [45]. In vitro, the equivalent of therapeutic doses of paracetamol can reduce intracellular concentrations of GSH in human alveolar macrophages which, in antigen presenting cells, leads to preferential Th2 cytokine

responses [89]. Another possibility is that acetaminophen causes airways epithelial damage through its actions as a selective cyclooxygenase-2 (COX-2) inhibitor, since it has been proposed that COX-2 plays an important role in repair of damaged airway epithelium [116]. Recently, a novel mechanism has been proposed. A study in mice showed that the equivalent of therapeutic doses of acetaminophen produced detectable concentrations of NAPQI in the lung. NAPQI in turn, stimulated the transient receptor potential ankyrin-1 (TPRA1) which caused neurogenic airway inflammation [78]. Finally, about the mechanisms operating prenatally, Henderson and Shaheen [45] speculated that acetaminophen crosses the placenta and the foetus is capable of generating NAPQI in late gestation. Future research should be directed towards establishing robust experimental evidence of the association between paracetamol and asthma, including the size of the effect and the estimated population-attributable benefit arising from interventions to modify paracetamol use in different groups [45].

Elements of pharmacodynamics: toxicity

The toxicity of paracetamol is closely linked to its metabolism. With therapeutic dosing, paracetamol is predominantly metabolized by glucuronidation and sulfation. Approximately 5 % to 10 % of the drug is oxidized by CYP450-dependent pathways to NAPQI. NAPQI is detoxified by glutathione and eliminated in the urine or bile. The NAPQI that is not detoxified may bind cysteine groups on proteins forming paracetamol–protein adducts in the liver [51]. High levels of adducts correspond to liver toxicity in patients with paracetamol-related acute liver failure [51]. Probably the NAPQI causes damage through binding mitochondrial proteins. This binding leads to decreased mitochondrial respiration, increased oxidative stress, and then to hepatic cellular necrosis [68]. Reports of liver toxicity in pediatric patients have suggested that a minimal, single paracetamol dose of 120–150 mg/kg (the normal dosage is 20 mg/kg) of body weight may be associated with hepatotoxicity [2, 46].

Hepatotoxicity after therapeutic dosing of paracetamol in children is rarely reported in defined-population studies. Case reports suggest that this phenomenon may occur, but few reports contain sufficient data to support a probable causal relationship [64]. Other reported cases of severe hepatotoxicity in children have been attributed to cumulative toxicity from repeated doses rather than acute intoxication from a single massive overdose [98]. Reports of hepatotoxicity in association with dosages reported to be in therapeutic range [47, 65] may represent inaccurate memory of administered doses or a narrower paracetamol therapeutic window because of associated conditions (Tables 1 and 2). Theoretically, not only an inherited but also an acquired higher activity of

Table 1 Conditions and situations that may increase the risk of paracetamol toxicity also with therapeutic dosing

Conditions and situations
Diabetes mellitus [106]
Obesity [81]
Chronic undernutrition [123]
Prolonged fasting [118]
Family history of hepatotoxic reaction [7]
Myopathies [25]
Inherited or acquired higher activity of CYP2E1 [111]

CYP2E1 could increase conversion of paracetamol to NAPQI [111] (Table 1). In fact, children with a family history of hepatic toxicity to paracetamol have an increased risk to develop a toxic reaction [7].

The kidney is the second target organ of paracetamol toxicity: renal dysfunction occurs in about 25 % of cases with significant hepatotoxicity and in more than 50 % of those with hepatic failure [94]. However, renal impairment after acute paracetamol overdose may also occur in the absence of hepatotoxicity [23].

Renal dysfunction after acute paracetamol overdose is the result of the local formation of NAPQI, that causes tubular necrosis [94]. However, several other nephrotoxic mechanisms have been proposed [35], because acute renal failure has been reported despite adequate treatment with *N*-acetylcysteine (NAC) [35]. Renal damage is also produced by chronic use of paracetamol, it has been showed a dose-dependent relationship between heavier paracetamol use and an increased risk of end-stage renal disease [87].

Conditions, situations and concomitant drugs that may increase the risk of paracetamol toxicity with therapeutic dosing

Since the NAPQI formation rate is related to acetaminophen toxicity, some situations, conditions (Table 1) or drugs (Table 2) could lead to increased risk of paracetamol toxicity by increasing formation of NAPQI or reducing glutathione stores.

Table 2 Drugs that can stimulate higher activity of CYP2E1 with increased conversion of paracetamol to NAPQI

Drugs
Carbamazepine [7]
Ethanol [99, 118]
Isoniazid [26, 75, 99]
Phenobarbital [7]
Rifampin [7]

Fasting is associated with increased paracetamol hepatotoxicity in humans [118] and animals [71] apparently because of increased metabolism to NAPQI [22, 97]. Protein-caloric malnutrition [123], obesity [81] and poorly controlled diabetes [106] are associated with increased activity of CYP2E1 that may increase formation of NAPQI (Table 1).

Detoxification may be reduced in patients with chronic protein-caloric malnutrition, who also have low glutathione levels [101].

Numerous drugs (Table 2) may affect paracetamol elimination or NAPQI detoxification and some of their effects on CYP2E1 activity are variable. Isoniazid first inhibits then enhances NAPQI formation as it is cleared [26, 75, 99]. Ethanol ingested chronically increases CYP2E1 activity and depletes glutathione, which enhances susceptibility to paracetamol toxicity [7, 75], whereas acute ethanol ingestion reduces paracetamol toxicity through competitive inhibition of CYP2E1 [6, 99].

Concurrent treatment with one or more of the drugs listed in Table 2 may be quite common among children with chronic illnesses. Adequate dosage and length of treatment should be considered in these cases [6, 71, 98, 118]. Whether hepatic injury from underlying conditions, such as viral infections or metabolic diseases, is exacerbated by paracetamol remains uncertain [7]. However, some studies show that an underlying condition can increase the risk of hepatic injury. For example, Ceelie et al. [25] showed that some children with myopathies receiving recommended doses of paracetamol might be at increased risk for development of toxicity resulting in acute liver failure.

Clinical presentation of paracetamol intoxication

Paracetamol intoxication typically includes four phases [7].

The first consists of anorexia, nausea, vomiting, malaise, and diaphoresis, which may provoke administration of additional doses of paracetamol. In the second phase, the first-phase signs resolve and are replaced by right upper quadrant pain or tenderness, liver enlargement, and oliguria in some patients. Bilirubin, hepatic enzyme levels and the prothrombin time increase. In the third phase, usually 3 to 5 days into the course, anorexia, nausea, vomiting, and malaise reappear, along with signs of hepatic failure, including jaundice, hypoglycemia, coagulopathy, and encephalopathy. Renal failure and cardiomyopathy may also develop. The fourth phase is associated with recovery or progression to death from complete liver failure. Paracetamol poisoning may also present with central nervous system depression, shock, hypothermia, and metabolic acidosis [38].

Paracetamol toxicity treatment

With acute ingestion of paracetamol, the Rumack–Mathews nomogram is a valuable tool to assess the risk of

hepatotoxicity [88, 96]. Overdose with intravenous paraceta-mol poses a specific management problem, as standard nomo-grams cannot be directly applied. In intravenous paracetamol overdose plasma levels peak immediately after intravenous injection, and will normally be lower than predicted from the same oral dose at the same time after ingestion. Guidance on management of IV paracetamol overdose is available from the UK National Poisons Information Service (NPIS), and is up-date regularly on Toxbase, the database of the NPIS (http://www.toxbase.org). IV paracetamol is potentially very toxic in overdose and managing clinicians are encouraged to discuss all patients with overdose with the local poisons information service.

Treatment is based on the use of NAC. A dose of activated charcoal is recommended within 6 to 8 h after an acute ingestion [88].

Intravenous administration of NAC over a 10-h period (rapidly) is associated with a higher frequency of allergic and anaphylactoid reactions (angioedema, hypotension, bron-chospasm) [96] than is oral administration. Longer infusion periods (48 h or longer) of NAC result in improved tolerance and reduced adverse effects [88].

The treatment of hepatotoxicity caused by subacute overdosing is difficult and consultation of an expert should be considered.

Paracetamol and fever

Fever is one of the most common clinical symptoms managed by pediatricians and other health care providers and accounts, by some estimates, for one-third of all presenting conditions in children [31]. Fever is not an illness but a physiologic homeo-static mechanism that has beneficial effects in fighting infec-tions [50]. Fever retards the growth and reproduction of bac-teria and viruses, enhances neutrophil production and T-lymphocyte proliferation, and aids in the body's acute-phase reaction [1]. The degree of fever does not generally correlate with severity of illness [1]. Moreover, the majority of evidence indicates that clinicians cannot rely on response to antipyretics to predict serious illness in febrile children [55]. Recent data on outcomes of meningitis, showed no improvement in pa-tients treated with paracetamol in addition to antimicrobials compared with placebo in addition to antimicrobials [86, 113]. Other studies showed also poorer outcomes in patients with sepsis and bacteremia treated with other NSAIDS compared with patients treated with paracetamol [59, 60]. In patients with sepsis, the paracetamol may inhibit the immunological response [52]. Therefore, clinicians should be aware of the potential side effect to treat fever in infectious diseases in terms of poorer outcome of the patients treated with antipyretics.

The most consistently identified serious concern of care-givers and health care providers is that high fevers, if left

untreated are associated with seizures, brain damage and death [17, 92].

It is argued that by creating undue concern over these presumed risks of fever, for which there is no clearly established relationship, physicians are promoting an exag-gerated desire in parents to achieve normothermia by aggres-sively treating fever in their children. Moreover, there is no evidence that antipyretic therapy decreases the recurrence of febrile seizures [108].

In view of this, it is recommended to treat only children with fever who appear distressed [112]. It could be also useful to treat febrile children with concomitant drowsiness to dis-cern if this condition is related simply to the fever or a potentially severe illness. Paracetamol doses of 5–15 mg/kg per dose given every 4 to 6 h orally or 15 to 20 mg/kg rectally are generally regarded as safe and effective (maximum dose 75 mg/kg/day) [103]. A dose of 90 mg/kg/day is considered by many authorities to be the definition of "supra-therapeutic dosing" [64, 103]. Typically, the onset of an antipyretic effect is within 30 to 60 min; approximately 80 % of children will experience a decreased temperature within that time [103, 109]. Although alternative dosing regimens have been sug-gested [77, 102, 110], no consistent evidence has indicated 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 con-fusion leading to hepatotoxicity; therefore, such doses are not recommended [109].

Nabulsi et al. [77] showed that standard (15 mg/kg) oral, standard (15 mg/kg) rectal and high-rectal (35 mg/kg) para-cetamol have similar antipyretic effectiveness. The effect compartment concentration of paracetamol that is sufficient for antipyretic effect is 5 mg/l (Fig. 3) [40] and this level is obtainable with rectal administration at standard dose. Much higher and not safe doses would be required for higher effect compartment concentrations and therefore, high-rectal dose should not be administered.

Moreover, there is no evidence to support the belief that rectal suppositories, whether prescribed in the standard dose of 15 mg/kg, or in the high dose of 30–40 mg/kg, are superior to oral paracetamol in terms of rapidity of action, or in the extent of temperature reduction [77]. The oral route should be preferred because of its predictable rapid absorption while the rectal route is effective in fever treatment in case of vomiting, or conditions preventing oral administration [77, 102]. Use of IV paracetamol is safe [124] and should be restricted to cases in which the oral or rectal route is not suitable.

A practice frequently used to control fever is the alternating or combined used of paracetamol and ibuprofen. Although 4 h was the most frequent interval, parents reported alternating therapy every 2, 3, 4, and 6 h, which suggests that there is no consensus on dosing instructions [120].

Some studies provide some evidence that combination therapy may be more effective at lowering temperature, questions remain regarding the safety of this practice as well as the effectiveness in improving discomfort [44, 57, 76, 85, 120]. There is no evidence that combination therapy results in overall improvement in other clinical outcomes. Therefore, the evidence to support or refuse the routine use of combination treatment with both paracetamol and ibuprofen are insufficient [109].

The NICE, in the updated guidance to help assess children with fever of May 2013, advises against giving both agents simultaneously and only considers alternating these agents if the distress, related to febrile condition, persists or recurs before the next dose is due [112].

Paracetamol and pain

Pain is a common condition in children and occurs predominantly during infectious illnesses, musculoskeletal injuries and after painful procedures or surgery.

Timely administration of analgesia affects the entire medical experience and can have a lasting effect on a child's and the family's reaction to current and future medical care [36].

Recommended paracetamol doses for pain management are given in Table 3 [122].

Paracetamol is the drug of choice for the management of mild to moderate pain and the management of moderate to severe pain with adjunctive opioid analgesics.

A large number of studies have been performed comparing paracetamol with NSAIDs for either analgesia or antipyresis in children. Most studies show either a similar effect or a slight superior effect of NSAIDs but one major criticism of such studies is that paracetamol dosing may not be equipotent with that of NSAID used [8]. Paracetamol has a better safety record for treatment of fever and pain related to upper airways infection since NSAIDS carry a higher risk of gastritis and renal impairment [18, 74]. NSAIDS showed to be superior for the treatment of muscle-skeletal traumatic pain [3, 27], and for the treatment of headache [67].

The rectal administration should be avoided in pain management because the effect compartment concentration of paracetamol required for analgesic effect is 10 mg/l (Fig. 2) [40]. This value is obtainable with oral administration at recommended doses of 15–20 mg/kg [122], but to obtain these levels with rectal route, it has been shown that the dose of rectal paracetamol should be greater than 40 mg/kg [40]. This dose exposes to a major risk of toxicity [103].

The US Food and Drug Administration approved IV paracetamol in January 2011 for short-term use in relieving moderate to severe pain. An intravenous paracetamol use is approved in children 2 years of age and older for the treatment of

Table 3 Recommended paracetamol doses for pain management (modified from ref. [122])

	Single initial dose at start of therapy (mg/kg)	Follow-on dose (mg/kg)	Dose interval (h)	Max. daily dose (mg/kg/day)
Rectal (do not prefer this route; see text)				
Premature infants 28th–30th GW	20	15	12	35
Premature infants 31st–38th GW	20	15	12	45
Newborn and infants up to 6 months	30	15	8	60
Infants after 6th month	35–45	15–20	6–8	60
Young children >1 year	35–45	15–20	(4–)6	75
Children >6 years	35–45	15–20	(4–)6	90 Absolute maximum 4,000 mg/day
Oral				
Newborn and infants up to 6 months	20	20	8	60
Infants after 6th month	30	10–20	(4–)6	60
Young children >1 year	30	15	(4–)6	75
Children >6 years	30	15	(4–)6	90 Absolute maximum 4,000 mg/day
Intravenous				
Term newborn infants, infants, toddlers and children weighing <10 kg[a]	7.5	7.5	(4–)6	30
Children weighing >10 kg	15	15	6	60 Absolute maximum 4,000 mg/day

[a] The dose of IV paracetamol is controversial in neonates and infants. The BNF for Children suggests a dose of 7.5 mg/kg every 8 h (maximum 25 mg/kg daily) in preterm neonates over 32 weeks postmenstrual age, 10 mg/kg every 4–6 h (maximum 30 mg/kg daily) in neonates

pain at a dose of 15 mg/kg every 6 h, not to exceed 75 mg/kg/day [34].

In the management of severe pain, the IV route could be preferred since it has a faster onset and results in more predictable pharmacokinetics than oral or rectal paracetamol formulations [16].

In the absence of iatrogenic medication error events, the IV use for the pain treatment is safe and effective [124].

Moreover, this formulation represents an attractive alternative or support with a dose sparing effect to IV opioids and non-steroidal anti-inflammatory drugs. Korpela et al. [56] showed that a single dose of 40 or 60 mg/kg of rectal paracetamol has a clear morphine-sparing effect in day-case surgery in children if administered at the induction of anesthesia. A meta-analysis of Remy et al. confirmed the morphine-sparing effect showing that paracetamol combined with patient-controlled analgesia morphine induced a significant morphine-sparing effect but did not change the incidence of morphine-related adverse effects. Ceelie et al. [24] in a recent randomized controlled trial showed that among infants undergoing major surgery, the addition of postoperative intermittent intravenous paracetamol to continuous morphine infusion compared with continuous morphine only resulted in a lower cumulative morphine dose over 48 h and a lower incidence of apnea and use of naloxone.

Finally, combination therapy with modest doses of paracetamol and ibuprofen has been shown to achieve as effective analgesia as single drug therapy with higher doses [69], while combination therapy with higher doses may increase propensity to adverse effects without analgesic gain [43].

Conclusions

Paracetamol is widely used but its analgesic mechanisms of action are still not well known. Paracetamol doses are different when treating fever or pain. Rectal administration of paracetamol should be avoided in pain management. While being a safe and effective drug it is important to optimize its administration to avoid overdoses and maximize effect. Fever phobia should be avoided and rationalized. Possible factors for increased risk of toxicity should be well known to the general pediatrician.

Conflict of interest   None.

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