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Review Article

Is Paracetamol (Acetaminophen) Still a First Line Option for Pain and Fever in Paediatrics?

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Abstract

Aim: This work was performed to provide updated information regarding the use of particularly oral paracetamol in children. **Methods:** The review was based on a comprehensive bibliographic search on paracetamol analgesic and antipyretic oral use in children from birth to adolescence. **Results:** The analgesic efficacy of paracetamol 15 mg/kg every 6 hours was demonstrated in headache/migraine, traumatic pain, Ear, Nose and Throat (ENT) conditions as pharyngotonsillitis, acute otitis media, sore throat pain or tonsillectomy and post-operative pain following dental extraction. Due to its central COX-independent antinociceptive action, paracetamol could be preferred to NSAIDs for mild-to-moderate acute pain. Its antipyretic efficacy was also demonstrated in several studies. Overall, paracetamol is safe in children, and undesirable effects at therapeutic doses are rare. **Conclusions:** The efficacy and safety of paracetamol in children are well known, and this drug can be used in children even from birth. This molecule is therefore recommended by main Scientific bodies as first line treatment for pain or fever in children.

Keywords: Paracetamol; Paediatrics; Pain; Fever

Key Notes

- Paracetamol has been used in children for a long time
- Its efficacy and safety in children from birth are well known
- It is recommended by main Scientific bodies as first line treatment for pain or fever in children

Introduction

Although paracetamol was discovered over 100 years ago and has been widely used in medical practice, its mechanism of action is still under debate. It has analgesic and antipyretic properties similarly to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), but, does not possess anti-inflammatory activity [1]. A growing body of evidence challenged the notion that paracetamol exerts its analgesic effect through Cyclooxygenase (COX)-dependent inhibitory effect. It is now admitted that paracetamol analgesic effect has multiple pathways. The main one is mediated by the formation of the bioactive AM404 metabolite in the Central Nervous System (CNS) with reinforcement of the activity of the descending serotonergic pathways. This mechanism is COX-independent, as opposed to NSAIDs [2]. Its antipyretic mechanism of action is thought to act centrally to convert the active oxidized form of COX in its inactive reduced form. 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 [3].

Paracetamol is indicated in children for mild to moderate pain and/or febrile conditions from birth, and paediatric formulations are convenient for children up to 12 years of age.

The recommended dosage of paracetamol is around 60 mg/kg/day, to be split in 4 intakes of 15 mg/kg with 6-hour intervals. This dosage was supported by a review of 53 published and unpublished clinical trials that evaluated antipyretic efficacy of paracetamol in over 3000 children [4]. The choice of this dosage is mainly due to safety purpose, as the Interpretation of analgesic and antipyretic responses documented after paracetamol administration is confusing because the response is not directly related to concentration in the blood, but rather to an effect compartment [5].

Although paracetamol is available for children using different routes for administration, this work only reports data with the oral route, as the rectal one is associated with a large variability in pharmacokinetics, i.e. delayed and erratic absorption [6], and a risk for not reaching therapeutic concentration [7]. The intravenous route is mainly indicated in case of need for emergency treatment of pain and/or when the other routes are not available. It is also used, although off label use, for closure of patient ductus arteriosus in neonates.

Materials and Methods

This work is based on a comprehensive bibliographic search of updated information on paracetamol in children.

The initial bibliographic searches were conducted via PubMed in November 2019 using the following: paracetamol and pain AND (Clinical Trial[ptyp] AND Humans[Mesh] AND English[lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])). This led to an initial selection of 536 publications; Paracetamol and fever AND (Clinical Trial[ptyp] AND Humans[Mesh] AND English[lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])) This led to an initial selection of 81 publications. After verification of the publication selection criteria (treatment of mild to moderate pain and/or fever; children; oral; dose around 15mg/kg every 6 hours), 14 publications were considered relevant.

Complementary searches were performed for the period December 2019 to December 2022 using the same process. They retrieved 420 publications for pain and 146 publications for fever. After verification of the publication selection criteria, no publication was considered relevant.

Additional searches using the same key words and looking for reviews on the period up to December 2022 led to an initial selection of 288 publications, out of which 14 were considered relevant. Additional search regarding recommendations retrieved 24 publications.

Additional specific searches were performed regarding paracetamol safety, and additional publications were retrieved using the references included in the selected publications.

Finally, a final selection of publications was performed in order to only keep the most recent and relevant ones.

Results

Paracetamol and Pain in Children

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [8]. However, the assessment of pain in children is complex, specifically in young children. No verbal assessment tools are available at that age; therefore, the assessment relies mainly on physiologic and behavioural responses to pain [9]. But adequate management of pain is mandatory, as it is well-known that excessive or maintained pain exposure can be detrimental and cause long-term consequences, especially in neonates who may suffer from hyperalgia and allodynia after experiencing pain [9]. The analgesic efficacy of paracetamol was shown in different painful conditions in children.

Paracetamol demonstrated its efficacy vs placebo in migraine/headache in children above 4 years in a randomised, double-blind, 3-way crossover study. This study included 88 children with migraine, aged from 4 to 16 years, who received in random order a single oral dose of 15 mg/kg paracetamol, 10 mg/kg ibuprofen and placebo, at home. A reduction in severe or moderate headache (grade ≥3 on a scale from 1 to 5) of at least 2 grades after 2 hours was reached twice as often with paracetamol as with placebo [10]. This efficacy was confirmed in multiple reviews that concluded that paracetamol is one of the first-line acute/rescue treatment for migraine headache in children [11,12]. In addition, it is also recommended for children treatment of migraine/headache by Scientific bodies as the French Society for the study of migraine and headache [13], or the American Academy of Neurology (AAN) [14].

The efficacy of paracetamol for traumatic pain in children above 4 years of age was demonstrated in one prospective, comparative, randomised study vs active comparator (ibuprofen). A total of 72 children aged 5-14 years seeking care with an acute limb fracture were analysed. They were randomised to receive 15 mg/kg paracetamol every 4 hours or 10 mg/kg ibuprofen every 8 hours. Child-reported pain scores decreased in both groups over a 48-hour period, with no difference between treatments [15]. The NICE guidelines recommend the use of oral paracetamol, or oral ibuprofen or both for pain in children with suspected long bone fractures [16].

Paracetamol is also recommended as first choice medication for acute and chronic pain associated with haemophilic arthropathy in children [17]. Studies and reviews in Ear-Nose-Throat (ENT) diseases have shown the efficacy of paracetamol for pharyngotonsillitis. In one prospective, comparative, randomised, placebo-controlled clinical study, 97 children were randomised to receive a single dose of 12 mg/kg paracetamol or placebo (double-blind), or 40 mg ketoprofen (open label). The administration of paracetamol was significantly more effective than placebo for the sum of pain intensity differences (SPID) at 1 hour, and patients treated with ketoprofen showed a similar improvement in pain over time [18]. Paracetamol was also effective for pain associated with Acute Otitis Media (AOM), and a Cochrane review concluded that paracetamol is more effective than placebo in relieving AOM pain at 48 hours [19]. Paracetamol was also recommended for regular administration in case of pain following post-tonsillectomy analgesia [20].

The interest of paracetamol as part of multimodal analgesia for post-operative pain in children was confirmed in the recommendations of the American Pain Society (APS). Paracetamol and NSAIDs have different mechanisms of action and research indicates that the combination of paracetamol with NSAIDs might be more effective than either drug alone. In addition, in patients also receiving opioids for management of postoperative pain, most studies show use of paracetamol or NSAIDs in conjunction with opioids is associated with less postoperative pain or opioid consumption than opioids alone [21]. In a review and meta-analysis of 3 clinical studies, 2 for post-extraction dental pain and 1 for sore throat pain, a single dose of paracetamol (7-15 mg/kg) showed comparable efficacy for moderate to severe pain as ibuprofen (4-10 mg/kg) [22].

On a more general basis, paracetamol was recommended as first choice analgesic in children by the Royal College of Emergency Medicine in 2017 [23]. Following codeine withdrawal, paracetamol was recommended for use as first line in case of mild to moderate pain in children by the French Haute Autorité de Santé (HAS) [24]. In 2020 and 2023, the French Health Authorities (ANSM) recommended paracetamol to be preferred vs NSAIDs, especially ketoprofen and ibuprofen, in case of pain and/or fever, particularly in an infection context as tonsillitis, otitis, cough, pulmonary infection, cutaneous infection or chicken pox, especially in case of self-medication [25,26].

There is little information available on paracetamol analgesic efficacy for painful conditions in children below 4 years of age, and the tested mode of administration was pre-emptive.

Paracetamol analgesic efficacy was assessed in clinical studies with pre-emptive administration before circumcision and before possible procedural pain. In a prospective, randomised, double-blind, placebo-controlled study, 44 neonates received either 15mg/kg paracetamol or placebo every 6 hours for 24 hours, starting 2 hours before circumcision. The assessment of pain was based on physiological data. Paracetamol did not demonstrate any improvement in intra-operative or postoperative pain, although it seems that it may provide some benefit after the immediate postoperative period [27]. In a non-randomised comparative study, 25 male new-borns received a single preoperative dose of 40 mg paracetamol vs 27 who did not receive any analgesia or anaesthesia. The assessment was based on behavioural observation and physiologic monitoring. The efficacy assessment was controversial with improvement in some parameters (limb movements, facial expression, breathing quality) and impairment in others (crying). The authors concluded that paracetamol could be helpful, even if the analgesic efficacy was not conclusive [28]. The same conclusion was provided by two reviews assessing different methods for pain prevention during neonatal male circumcision [29,30]. The efficacy of pre-emptive administration of paracetamol for procedural pain was assessed in a comparative study vs placebo: In a prospective, comparative, randomised, placebo-controlled study which assessed the efficacy of paracetamol in reducing pain during examination for retinopathy of prematurity included 114 infants. They received a single dose of either 15mg/kg paracetamol or a placebo 60 minutes before examination. Topical anaesthetic was applied in addition to all infants. A significant decrease in the premature infant pain profile was shown in the paracetamol group, while there were no differences regarding crying time and the number of infants with tachycardia/bradycardia and desaturation [31]. A review examining the drugs for analgesia in the neonatal intensive care unit (ICU) recommended the use of paracetamol [32]. This use of paracetamol is also recommended for neonatal pain by the National Health Service (NHS) Greater Glasgow and Clyde guidelines [33], and by American experts [34].

Paracetamol and Fever in Children

Fever is one of the most common clinical reasons for paediatric consultations, accounting for about one-third of all presenting conditions in children [35]. It is not an illness but a physiological mechanism that has beneficial effects on fighting infection [3] and is a response to diseases or invasions by pathogens. The physiological mechanisms that result in fever is not clear. However, several immunological factors are known to interact in the process that leads to fever, including the chemical factors called cytokines produced by white blood cells. Experts suggest that cytokines act on temperature-regulating center of the brain (thermoregulatory center) to initiate the physiological responses that triggers fever [36].

In children above 6 months, the efficacy of paracetamol was demonstrated in one comparative study vs placebo, and 1 study vs ibuprofen as active comparator. The prospective, comparative, randomised, placebo-controlled study investigated the antipyretic

efficacy of 15mg/kg paracetamol administered every 6 hours in 210 children from 6 months to 6 years. Paracetamol resulted in a significantly higher decrease of temperature during the first hours following drug administration, and, at 4 hours, the rate of afebrile children was 47% in the paracetamol group vs 12% in the placebo group ($p<0.001$) [37]. Another prospective, comparative, randomised, double-blind, double-dummy study was performed in 199 hospitalised children (6 months-12 years) with fever of likely infectious origin. They received a single dose of either 10.6mg/kg paracetamol or 6.7mg/kg ibuprofen. There were no differences between the 2 treatments and the maximal temperature decrease was observed at 2 hours in both groups [38]. This efficacy was confirmed in literature reviews and meta-analyses, which concluded that the antipyretic efficacy of paracetamol was similar to ibuprofen, but that paracetamol was safer [3,39].

Febrile seizures are the most common form of childhood seizure, usually occurring between 6 months and 5 years of age. A small cohort of children develop febrile seizures (2-5% in the West), while the greater majority will not. A febrile seizure is due to a brain's aberrant response to high temperature and not a response to an infection. While the underlying brain disorder appears to have no significant adverse implication in the majority of children with febrile seizures, serious long-term outcomes (cognitive and neuropsychiatric) have been recently reported, including sudden death. These adverse events likely reflect the underlying intrinsic brain pathology, as yet undefined, of which febrile seizures are purely a manifestation and not the primary cause (Mewasingh, 2020).

A systemic review and meta-analyses reported by Hashimoto et al. in 2020 showed that only one study reported that antipyretics prevented the recurrence of febrile seizures within the same fever episode (9.1% in the acetaminophen group vs. 23.5% in the control group, $p<0.01$). This review provides very limited support for the use of antipyretics in preventing febrile seizure recurrence within the same fever episode and no evidence for its use in distant fever episodes. New studies are required to evaluate this topic further and determine whether the effectiveness of antipyretics is based on intervention timing (Hashimoto, 2020).

There is no clinical data available in the literature regarding oral or rectal paracetamol as antipyretic in neonates, but one retrospective analysis of safety and efficacy of IV propacetamol or paracetamol in normothermic and febrile neonates showed a significant decrease in body temperature [40].

The use of paracetamol as antipyretic for children is recommended by the American Academy of Pediatrics (AAN) [41], the English scientific society, NICE [42], and the French scientific society, HAS. For HAS, paracetamol should be used as first line, and NSAIDs should be used only in case of contra-indication to paracetamol. Ibuprofen and Ketoprofen should not be used for ages under 3 months and 6 months respectively [43]. As for its analgesic use, due to the risk of symptom hiding in case of bacterial infection, the French Health Authorities recommended paracetamol over NSAIDs in case of pain and/or fever, particularly in an infection context as tonsillitis, otitis, cough, pulmonary infection, cutaneous infection or chicken pox, especially in case of self-medication [25,26].

Paracetamol Safety in Children

Paracetamol is a safe drug at appropriate doses and the potential toxicity is closely linked to its metabolism [44]. At therapeutic doses, undesirable effects are rare [1], or of low impact in children [45].

As exposed above, paracetamol mechanism of action is different from the NSAIDs mechanism which is peripheral COX-dependent. Therefore, its safety profile is different in comparison with NSAIDs, known to have much more safety concerns or side effects (gastric ulcers and bleeding, bronchial asthma, acute kidney injury, and long-term adverse cardiovascular outcomes).

In addition to the adverse events reported in paracetamol information notice, i.e. rare cases of hypersensitivity, very rare cases of serious cutaneous reactions, thrombopenia, leukopenia and neutropenia, a possible link between paracetamol intake and the occurrence of some events was questioned in the literature.

The hepatotoxicity of paracetamol is caused by the formation of a toxic metabolite, N-Acetyl-P-Benzoquinoneimine (NAPQI) in case of overdosage [46]. Paracetamol is metabolized in the liver mainly through glucuronidation, sulfation, and to a lesser extent oxidation. Because of the difference in the ontogeny of various metabolizing pathways, the relative contribution of each pathway to the overall paracetamol metabolism in children changes with age. The sulfation pathway plays a more important role in metabolizing paracetamol than the glucuronidation pathway in younger children as compared with older children and adults [47]. At therapeutic doses, some isolated cases of elevated transaminases were described in children following the administration of paracetamol [48]. However, there was no evidence of increased hepatotoxicity with therapeutic dose.

The risk of hospitalization from acute GI bleeding, was measured in a randomized control trial of 84 192 children receiving either paracetamol (12 mg/kg) or ibuprofen (5 or 10 mg/kg) as repeated doses at intervals of 4 to 6 hours, with a maximum of 5 doses per day. Among the 28 130 children randomized to paracetamol treatment, the risk was zero per 100 000 (95% CI 0 to 11 per 100 000) vs 7.2 per 100 000 (95%CI 2 to 18 per 100 000) for the 55 785 ibuprofen patients [49].

The same randomised study presented above provided information regarding renal safety, and there were no cases of renal failure in over 80 000 children treated with either ibuprofen or paracetamol [49].

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are known to be potential adverse drug reactions and were described as possibly associated with paracetamol use with a very low risk: Twenty case reports are available in the international literature, and a positive challenge was described for 2 of them. However, no obvious risk related to the use of paracetamol was found in a well-conducted analysis of a large pharmacovigilance series including both adults and children [50].

Controversial data may be found on the association of childhood asthma and paracetamol intake during childhood. A positive association was described in some publications [51,52], while a weak or no association was described in others [53,54]. It should be kept in mind that a definite conclusion may be difficult to draw as it is difficult to find children with no paracetamol administration during childhood.

Only inconclusive data are available on the role of paracetamol (mainly prenatal exposure) in the occurrence of Autism Spectrum Conditions (ASC) or Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms. This led to a collaborative study of 6 European population-based birth/child cohorts dedicated to study this association. In this study, postnatal (up to 18 months) exposure to paracetamol was not associated with ASC or ADHD symptoms [55].

The comparative safety of paracetamol and ibuprofen may be approached using the analysis of the Italian Spontaneous Reporting Database from Jan 2005 to April 2020 in children 0-17 years old [56]. Out of these patients reporting adverse events, there was a higher rate of patients reporting ibuprofen intake, 26%, than paracetamol intake, 15%.

Paracetamol overdose is a major cause of acute liver failure and is the most common identifiable cause of acute liver failure in children, with potentially toxic doses from 150 mg/kg and above [57]. However, probably due to the different liver metabolism in younger children as compared with older children and adults, with a more important sulfation than glucuronidation pathway [47], the rate of liver injury and hepatotoxicity in children is lower compared with adults following a single acute overdose; on another hand, the mortality in children may be high in case of multiple sequential overdoses [58]. To this respect, the Rumack–Matthew nomogram plots serum concentration of paracetamol against the time since ingestion, in order to predict possible liver toxicity [59]. Serum paracetamol concentration at (or as soon as possible after) 4 hours post ingestion determines the need for N-Acetyl Cysteine (NAC) administration, a safe and effective antidote.

Epidemiological studies indicate that prenatal exposure to paracetamol is associated with neurodevelopmental problems. Based on these studies, it can be concluded that prenatal exposure to paracetamol causes risks of developmental delays, attention deficit hyperactivity disorder, and a subtype of autism spectrum disorder (ASD) associated with hyperkinetic behavior. In contrast, data regarding postnatal exposure to paracetamol are limited (Patel 2022).

A systemic review was performed on neurodevelopment safety of paracetamol. 218 publications were identified that made claims that paracetamol was safe for use with infants or children. From these 218, a total of 103 papers were identified as sources of authority for the safety claim. A total of 52 papers contained actual experiments designed to test safety, and had a median follow-up time of 48 h. None monitored neurodevelopment. Furthermore, no trial considered total exposure to drug since birth, eliminating the possibility that the effects of drug exposure on long-term neurodevelopment could be accurately assessed. In 2019 the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessment stated that a large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity, and that epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency (PRAC 2019). On the other hand, abundant and sufficient evidence was found to conclude that paracetamol does not induce acute liver damage in babies or children when used as directed (Cendejas-Hernandez 2022).

Discussion

Pain management in children still needs to be improved, and there is evidence that infant pain is still under-managed or unmanaged [59].

In that context, the management of pain and fever should also encompass a non-pharmacological approach. Regarding drugs, future research would be advisable provide pediatric population with improved efficacy/safety ratio for analgesics. (A voir avec les experts).

To date, Paracetamol efficacy in children was demonstrated for mild to moderate pain in clinical studies. Even if the clinical development of paracetamol in children is not fulfilling current guidelines, clinical trials versus placebo provided information in multiple conditions, including migraine/headache, traumatic pain, ENT diseases and post-operative pain.

Paediatric clinical studies are always more difficult to perform, especially with a relevant assessment criterion for pain. The assessment of pain is complex, specifically in neonates, infants

and preschool-aged children, because the expression of pain is undifferentiated, and it is often difficult to distinguish between pain, irritability and anxiety [9]. Pain may be assessed in older children using well-described tools, including verbal scales, while its assessment in the youngest is difficult and often based on physiological, behavioural and bio-behavioural reactions [9]. The most frequent physiological indicators of pain are changes in heart and respiratory rate, blood pressure and oxygen saturation. These indicators may be affected by other physiological stimuli such as hypovolemia or fever. The most used behavioural indicators are crying, facial activity, agitation and sleeplessness, but other factors may also interfere [9]. This may explain why there are no publication of studies measuring paracetamol as treatment of pain in children below 4 years, and why there are only pre-emptive studies. It may also explain why the outcomes of these studies in young children are not convincing. For older children, pain assessment is less difficult, and the most commonly used scales for pain assessment include visual analogue scale, verbal numeric scale and graphic scales [9].

The analgesic efficacy of paracetamol should also be approached based on its efficacy in combination with opioids for reduction of opioid requirements [20,21].

In addition to the adverse events reported in paracetamol instruction notice, multiple works tried to provide additional information regarding the possible link between paracetamol intake during childhood and various conditions. This was the case for asthma or neurodevelopment. But no definite conclusion could be drawn out of these studies as they were most often large retrospective epidemiological studies in a context where it is difficult to find children with no paracetamol intake during childhood.

Paracetamol hepatotoxicity in case of overdosage is well known. However, it should be noted that accidents in children are rare, secondary to overdoses, either as a single intake, or as repeated increased dosing.

Several works regarding the mechanism of action of paracetamol led to identify a COX-independent mechanism of action for analgesia, different from NSAIDs'. This leads therefore for a better safety profile of paracetamol versus NSAIDs.

The good safety profile of paracetamol, used for many years in adults and in children, provides an interesting efficacy/safety balance, support of international guidelines recommending the use of paracetamol in children for mild to moderate pain.

As paracetamol and NSAIDs mechanism of action are different, in the cases where paracetamol or NSAIDs alone is not sufficient to decrease the pain, its combination with ibuprofen was demonstrated to be potentially more effective than either drug alone [21], and has been recommended [24]. Adequate management of infant and child pain is imperative and may include non-pharmacological analgesia in combination to pharmacological treatment.

There are few published data on paracetamol antipyretic efficacy. However, several studies vs placebo or active comparators demonstrated the antipyretic efficacy of paracetamol.

Although there may be physiologic benefits of fever, it may also be associated with apathy, anorexia, headache and decrease in activities, all signs of immune response. This situation may be considered as uncomfortable, and the objective of the treatment is to decrease this discomfort and not to normalise the temperature [43].

Fever phobia is a common world phenomenon that affected caregivers and healthcare providers (Clericetti 2019). Fever is a reliable sign of illness, but it also evokes fear and anxiety. It is not the fever itself but the fear of possible complications and accompanying symptoms that is important for paediatricians and parents. Paediatricians should focus on the monitoring of signs/symptoms of serious illness, improving the child's comfort by maintaining hydration, and educating parents about the appropriate use, dosage, and safe storage of antipyretics (Gunduz et al. 2016).

Due to the different mechanisms of action of paracetamol and NSAIDs, alternating ibuprofen and paracetamol is often used for antipyretic purposes and was shown to be more efficient than each drug alone [21]. However, practitioners who choose to follow this practice should counsel parents carefully regarding proper formulation, dosing, and dosing intervals [43]. The simultaneous use of paracetamol and ibuprofen is not recommended for fever in children below 5 years according to the NICE [42], The French Heath Authorities also recommend the use of a single antipyretic [43].

Conclusions

The efficacy and safety of paracetamol in children are well known, and this drug can be used in children from birth. Due to the lack of peripheral action on cyclooxygenases, the tolerance profile could be considered as better than NSAID which are not recommended in new-borns. Therefore, due to its good benefit/risk ratio, paracetamol is recommended as the first line treatment for pain and fever especially in very young children.

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References

1. Jozwiak-Bebenista M, Nowak JZ (2014) Paracetamol: mechanism of action, applications and safety concern. Acta Pol Pharm 71: 11-23.
2. Mallet C, Desmeules J, Pegahi R, Eschalier A (2023) An Updated Review on the Metabolite (AM404)-Mediated Central Mechanism of Action of Paracetamol (Acetaminophen): Experimental Evidence and Potential Clinical Impact. J Pain Res 16: 1081-1094.
3. Van den Anker JN (2013) Optimising the management of fever and pain in children. Int J Clin Pract Suppl (178): 26-32.
4. Temple AR, Temple BR, Kuffner EK (2013) Dosing and antipyretic efficacy of oral acetaminophen in children. Clin Ther 35: 1361-75.e1-45.
5. Gibb IA, Anderson BJ (2008) Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Chil 93: 241-247.
6. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP (1995) Plasma concentrations after high-dose (45mg.kg-1) rectal acetaminophen in children. Can J Anaesth 42: 982-986.
7. Anderson BJ, Woolard GA, Holford NH (1995) Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatr Anaesth 5: 237-242.
8. International Association for the Study of Pain (IASP) (2020) IASP announces revised definition of pain.
9. Mencia S, Alonso C, Pallas-Alonso C, Lopez-Herce J and maternal and child health and development network II (SAMID II) (2022) Evaluation and treatment of pain in fetuses, neonates and children. Children 9: 1688.
10. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P (1997) Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 48: 103-107.
11. Damen L, Bruijn JK, Verhagen AP, Berger MY, Passchier J, et al. (2005) Symptomatic treatment of migraine in children: a systematic review of medication trials. Pediatrics 116: e295-e302.
12. Patniyot IR, Gelfand AA (2016) Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic Review. Headache 56: 49-70.
13. Geraud G, Lanteri-Minet M, Lucas C, Valade D (2004) French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther 26: 1305-1318.
14. American Academy of Neurology (AAN) (2019) Practice guideline update: acute treatment of migraine in children and adolescents.
15. Shepherd M, Aickin R (2009) Paracetamol versus ibuprofen: a randomized controlled trial of outpatient analgesia efficacy for paediatric acute limb fractures. Emerg Med Australas 21: 484-490.
16. NICE guideline [NG38] (2016) Fractures (non-complex): assessment and management.
17. Gualtierotti R, Tafuri F, Arcudi S, Solimeno PL, Acquati J, et al. (2022) Current and Emerging Approaches for Pain Management in Hemophilic Arthropathy. Pain Ther 11: 1-15.
18. Ruperto N, Carozzino L, Jamone R, Freschi F, Picollo G, et al. (2011) A randomized, double-blind, placebo-controlled trial of paracetamol and ketoprofren lysine salt for pain control in children with pharyngotonsillitis cared by family pediatricians. Ital J Pediatr 37: 48.
19. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, et al. (2016) Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database Syst Rev 12: CD011534.
20. Walker SM (2015) Pain after surgery in children: clinical recommendations. Curr Opin Anaesthesiol 28: 570-576.
21. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, et al. (2016) Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 17: 131-157.
22. 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: 521-526.
23. Royal College of Emergency Medicine Best practice guideline. Management of pain in children.
24. HAS. Prise en charge médicamenteuse de la douleur chez l'enfant : alternatives à la codéine. Février 2016.
25. ANSM (2023) Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves – Point d'information. Actualisation May 2020.
26. ANSM. Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves. Actualisation du 27/04/2023.
27. Howard CR, Howard FM, Weitzman ML (1994) Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics 93: 641-646.
28. Malnory M, Johnson TS, Kirby RS (2003) Newborn behavioral and physiological responses to circumcision. MCN Am J Matern Child Nurs 28: 313-317.
29. Brady-Fryer B, Wiebe N, Lander JA (2004) Pain relief for neonatal circumcision. Cochrane Database Syst Rev 2004: CD004217.
30. Labban M, Menhem Z, Bandali T, Hneiny L, Zaghal A (2021) Pain control in neonatal male circumcision: A best evidence review. J Pediatr Urol 17: 3-8.
31. Kabatas EU, Dursun A, Beken S, Dilli D, Zenciroglu A, et al. (2016) Efficacy of Single Dose Oral Paracetamol in Reducing Pain During Examination for Retinopathy of Prematurity: A Blinded Randomized Controlled Trial. Indian J Pediatr 83: 22-26.
32. Hall RW, Shbarou RM (2009) Drugs of choice for sedation and analgesia in the neonatal ICU. Clin Perinatol 36: 15-26.
33. NHSGGC paediatrics for health professionals. Neonatal pain guideline.
34. Witt N, Coynor S, Edwards C, Bradshaw H (2016) A guide to pain assessment and management in the neonate. Curr Emerg Hosp Med Rep 4: 1-10.
35. Chiappini E, Bortone B, Galli L, de Martino M (2017) Guidelines for the symptomatic management of fever in children: systematic review of the literature and quality appraisal with AGREE II. BMJ Open 7: e015404.
36. Meremikwu MM, Oyo-Ita A (2002) Paracetamol versus placebo or physical methods for treating fever in children. Cochrane Database Syst Rev 2002: CD003676.
37. Gupta H, Shah D, Gupta P, Sharma K (2007) Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo controlled trial. Indian Pediatr 44: 903-911.
38. Nadal CF, de Miguel MJG, Campdera AG, Fernandez JP, Calatayud GA, et al. (2002) Effectiveness and tolerability of ibuprofen-arginine versus paracetamol in children with fever of likely infectious origin. Acta Paediatr 91: 383-390.

39. Kuo N, Su NY, Hou SK, Kang YN (2021) Effects of acetaminophen and ibuprofen monotherapy in febrile children: a meta-analysis of randomized controlled trials. Arch Med Sci 18: 965-981.

40. Hopchet L, Kulo A, Rayyan M, Verbesselt R, Vanhole C, et al. (2011) Does intravenous paracetamol administration affect body temperature in neonates? Arch Dis Child 96: 301-304.

41. Sullivan JE, Farrar HC (2011) Fever and antipyretic use in children. Pediatrics 127: 580-587.

42. Davis T (2013) NICE guideline: feverish illness in children--assessment and initial management in children younger than 5 years. Arch Dis Child Educ Pract Ed 98: 232-255.

43. HAS Haute Autorité de Santé. Prise en charge de la fièvre chez l'enfant. Octobre 2016.

44. Cuzzolin L, Antonucci R, Fanos V (2013) Paracetamol (acetaminophen) efficacy and safety in the newborn. Curr Drug Metab 14: 178-185.

45. Hartling L, Ali S, Dryden DM, Chordiya P, Johnson DW, et al. (2016) How Safe Are Common Analgesics for the Treatment of Acute Pain for Children? A Systematic Review. Pain Res Manag 2016: 5346819.

46. Ogilvie JD, Rieder MJ, Lim R (2012) Acetaminophen overdose in children. CMAJ 184: 1492-1496.

47. Ji P, Wang Y, Li Z, Doddapaneni S, Hertz S, et al. (2012) Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. J Pharm Sci 101: 4383-4389.

48. Savino F, Lupica MM, Tarasco V, Locatelli E, Garazzino S, et al. (2011) Fulminant hepatitis after 10 days of acetaminophen treatment at recommended dosage in an infant. Pediatrics 127: e494-e497.

49. Lesko SM, Mitchell AA (1995) An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 273: 929-933.

50. Lebrun-Vignes B, Guy C, Jean-Pastor MJ, Gras-Champel V, Zenut M (2018) Is acetaminophen associated with a risk of Stevens-Johnson syndrome and toxic epidermal necrolysis? Analysis of the French Pharmacovigilance Database. Br J Clin Pharmacol 84: 331-338.

51. Beasley R, Clayton T, Crane J, von Mutius E, Lai CKW, et al. (2008) Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet 372: 1039-1048.

52. Amberbir A, Medhin G, Hanlon C, Britton J, Davey G, et al. (2014) Effects of early life paracetamol use on the incidence of allergic disease and sensitization: 5 year follow-up of an Ethiopian birth cohort. PLoS One 9: e93869.

53. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, et al. (2010) Paracetamol use in early life and asthma: prospective birth cohort study BMJ 341: c4616.

54. Bakkeheim, E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC (2011) Paracetamol in early infancy: the risk of childhood allergy and asthma. Acta Paediatr 100: 90-96.

55. Alemany S, Avella-García C, Liew Z, García-Esteban R, Inoue K, et al. (2021) Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: meta-analysis on six European population-based cohorts. Eur J Epidemiol 36: 993-1004.

56. Pelliccia V, Rossi S, Zollino I, Quagliarella F, Buonocore G (2022) Adverse Drug Reactions of Acetaminophen and Ibuprofen in the Paediatric Population: Analysis of the Italian Spontaneous Reporting Database. Curr Pediatr Rev 18: 64-71.

57. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, et al. (2006) Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 148: 652-658.

58. Caparrotta TM, Antoine DJ, Dear JW (2018) Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. Eur J Clin Pharmacol 74: 147-160.

59. Rumack BH, Matthew H (1975) Acetaminophen poisoning and toxicity. Pediatrics 55: 871-876.