Career Point International Journal of Research (CPIJR)
©2022 CPIJR | Volume 3 | Issue 3 | ISSN: 2583-1895
July-September-2024 | DOI: https://doi.org/10.5281/zenodo.14029572

Paracetamol (Acetaminophen): An Intimate Drug with Unexplained Adverse Effects on Body

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Abstract

Paracetamol (acetaminophen) is the most used drug in the world, with a long record of use in acute and chronic pain. In recent years, the benefits of paracetamol use in chronic conditions has been questioned, notably in the areas of osteoarthritis and lower back pain. Over the same period, concerns over the long-term adverse effects of paracetamol use have increased, initially in the field of hypertension, but more recently in other areas as well. The evidence base for the adverse effects of chronic paracetamol use consists of many cohort and observational studies, with few randomized controlled trials, many of which contradict each other, so these studies must be interpreted with caution. Nevertheless, there are some areas where the evidence for harm is more robust, and if a clinician is starting paracetamol with the expectation of chronic use it might be advisable to discuss these side effects with patients beforehand. An increased risk of gastrointestinal bleeding and a small (~4 mmHg) increase in systolic blood pressure are adverse effects for which the evidence is particularly strong, and which show a degree of dose dependence. As our estimation of the benefits decreases, an accurate assessment of the harms is ever more important. The present review summarizes the current evidence on the harms associated with chronic paracetamol use, focusing on cardiovascular disease, asthma and renal injury, and the effects of *in utero* exposure.

Keywords: Paracetamol, Cyclooxygenase, Thermoregulation, Acetaminophen, Adverse effects.

Introduction

Paracetamol (acetaminophen, N-acetyl-*p*-aminophenol) is one of the most widely used over-the-counter analgesic antipyretic drugs. It was first synthesized by Joseph von Mering in (1893) by reacting *p*-nitrophenol with tin and glacial acetic acid. In the 1880s paracetamol and phenacetin figure(1) were found to possess antipyretic and later

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analgesic activity. Initially, phenacetin gained more popularity than paracetamol and was marketed in 1887; however, because of the serious side effects associated with phenacetin such as hemolytic anemia and methemoglobin formation, its clinical use declined, and attention focused on paracetamol, which was marketed in 1893 .

1. Additionally, more studies on phenacetin in the 1940s showed that paracetamol is one of its major metabolites and thus its pharmacological effects are attributed to paracetamol.
2. As a result, paracetamol became freely available from the 1950s and has become the most widely used over-the-counter non-narcotic analgesic agent for the treatment of mild to moderate pain and fever.

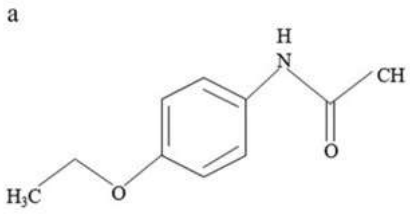

Figure 1: a. Paracetamol

Paracetamol now dominates the market of over-the-counter non-narcotic analgesic drugs following the demonstration of its safety profile at therapeutic doses and particularly after aspirin usage began to decline since the 1960s due to its gastrointestinal toxicity and association with Reye's Syndrome in children .

3. Today paracetamol is the standard and first-line treatment for fever and acute pain and is believed to remain so for many years to come .
4. This is mainly due to its outstanding safety record at therapeutic doses when compared to the non-steroidal anti-inflammatory drugs (NSAIDs). Sales of paracetamol, most widely consumed over-the-counter analgesic drug, have been on the increase for the past few years – a trend that it is predicted to continue.

The uses of paracetamol

Paracetamol was introduced into the pharmacological market in 1955 by McNeil aboratories as a prescribed analgesic and anupyretic drug lor children under its trade name Tvlenol Children's Bluxu (the name tvleno derives from its chemical name N-acetv-D-aminodheno. One vear later. 300-mg tablets or paracelamol were available over the counter in Great Britain under the trade name of Panadol, which were produced by

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Frederick Stearns & Co, the branch of Sterling Drug Inc. In Poland. paracetamo became available in 96 and since then it has belonged to the one of the most frequent-v sold analgesic medications. There are about a 100 preparations in the trade offer, which contain pard cetamol alone or in combination with other active.

The paracetamol place on the WHO analgesic ladder, which precisely defines the rules for applica-lion of analgesic drugs. is impressive. This drug has been placed on all three steps of pain treatment intensity. In different pains or moderate intensity. paracetamol as a weak analgesic together with non-steroidal analgesic drugs or co-analgesics e.g., caffeine) is a basic non-opioid analgesic (the first step of the analgesic ladder). When pain maintains or increases. paracetamol is used as an additional analgesic with weak (e.g., caffeine, tramadol) or strong (e.g. morphine. pentenyl) opioids from the second and third step of the analgesic ladder, respectively.

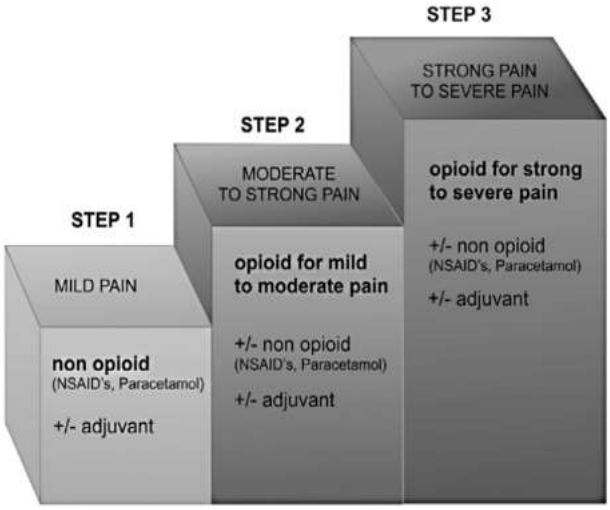

Figure 2: Paracetamol with WHO ladder

Paracetamol, if efficient, is a recommended oral analgesic of a first choice to be used for a long time, e.g., in symptomatic treatment of slight and moderate pain occurring in osteoarthritis as well as in muscle or tendon pains. Moreover, it is a drug of choice in patients in whom application of non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated, e.g., in the case of gastric ulcers, hypersensitivity to aspirin, impairments in blood coagulation, in pregnant women, nursing mothers and children with fever accompanying a disease (5).

The use of paracetamol in children requires special care and maintain in an adequate dosage (based on age), which significantly differs from standard adult.

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The recommended dosage for children considers the metabolism of paracetamol, which determines the toxicity of the drug, especially hepatotoxicity (see below). In children, paracetamol metabolism changes with age: in younger children the sulfation pathway is dominated route of paracetamol elimination (which is mature at birth); the glucuronidation pathway takes about two years to mature. The oxidation of paracetamol, which takes place mainly with the participation of the enzyme CYP2E1 in neonates is negligible, because the activity of CYP2E1 increases with age, reaching the adult value at age 1-10 years. For comparison, in adults, paracetamol is metabolized mainly in the liver via glucuronidation (50-60%), sulfation (25-30%) and oxidation (< 10%) (see below in the section on adverse effects). Therefore, according to Ji et al. (6), the proposed dosage of paracetamol in children up to 12 years is as follows:

- under 2 years - no recommended dose: treatment under the supervision of a physician;
- 2-3 years - 160 mg (daily dose divided into two dose units, i.e., 2 × 80 mg); total dose corresponds to 1/2 of a single dose for an adult, i.e., 325 mg;
- 4-6 years - 240 mg (daily dose divided into three dose units, i.e., 3 x 80 mg); total dose corresponds to 3/4 of a single dose for an adult;
- 6-9 years - 320 mg (daily dose divided into four dose units, i.e., 4 × 80 mg); total dose is the same as a single dose for an adult;
- 9-11 years - 320-400 mg (daily dose divided into four-five dose units, i.e., 4-5 × 80 mg; total dose corresponds to 1-1 1/4 of a single dose for an
- 11-12 years - 320-480 mg (daily dose divided in the four-six dose units, ie 4-6 × 80 mg; total dose corresponds to 1 - 1 1/2 of a single dose for an adult.

According to the 20th edition of Drugs of Contemporary Therapy (Polish), the acetaminophen dosage schedules in paediatric patients should be as follows: 10-15 mg/kg oral dose and 15-20 mg/kg rectal dose every 4-6 h, maximum of 5 doses/day; in newborns orally or rectally 10 mg/kg of body weight every 4 h or 15 mg/kg every 6 h (maximum daily dose in newborns is 60 mg/kg).(7)

Mechanisms of action

It is surprising that after more than 100 years, the exact mechanism of action of paracetamol remains to be determined. There is evidence for several central mechanisms, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide

(NO), and cannabinoid pathways, and it is likely that a combination of interrelated pathways are in fact involved. A few of these are outlined below (8,9)

Prostaglandin inhibition

Paracetamol is termed a simple analgesic and an antipyretic. Despite enduring assertions that it acts by inhibition of cyclooxygenase (COX)-mediated production of prostaglandins, unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol has been demonstrated not to reduce tissue inflammation. Two explanations have been put forward for this.

The enzyme responsible for the metabolism of arachidonic acid to the prostanoids (including prostaglandins and thromboxanes), commonly referred to as cyclooxygenase, is also more appropriately called prostaglandin H2 synthetase (PGHS), and possesses two active sites: the COX and the peroxidase (POX) sites. The conversion from arachidonic acid to the prostanoids is in fact a two-stage process, requiring activity at the COX site to first produce the unstable intermediate hydroperoxide, prostaglandin G2 (PGG2), which is then converted to prostaglandin H2 (PGH2) via POX. The enzymatic activity of COX relies on its being in the oxidized form and it is suggested that paracetamol interferes indirectly with this by acting as a reducing co-substrate at the POX site. In intact cells, when levels of arachidonic acid are low, paracetamol is a potent inhibitor of PG synthesis, by blocking the physiological regeneration of POX. However, in broken cells, where the concentration of hydroperoxides is high, prostaglandin synthesis is only weakly inhibited. This peroxidedependent COX inhibition explains the differential activity of paracetamol in the brain where peroxide concentrations are low, vs peripheral sites of inflammation with high peroxide levels as showed in figure 3.

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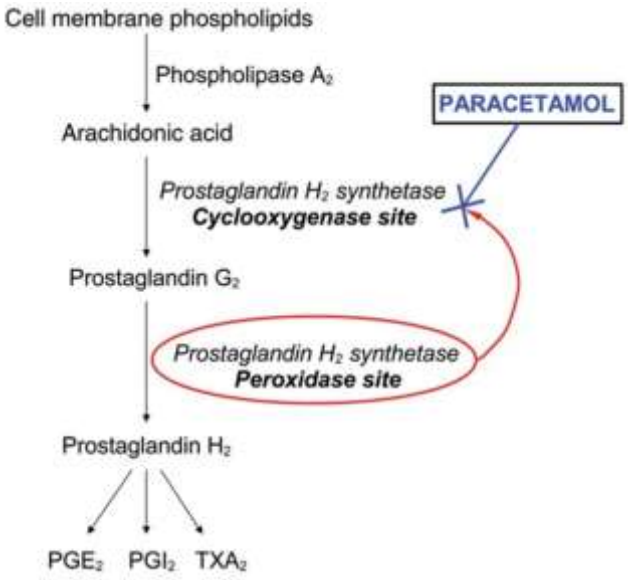

Figure 3: Role of paracetamol in inhibition of prostaglandin production.

An alternative suggestion was that, unlike NSAIDS, which act on COX-1 and -2, paracetamol may act on a discrete COX-1 splice variant (initially thought to be a distinct isoenzyme, COX-3). This COX-1 variant was thought to be active in the central nervous system, rather than at the site of injured or inflamed tissue, such that inhibition by paracetamol here would explain its lack of anti-inflammatory and anti-platelet activity, whilst still affording it highly effective analgesic and antipyretic properties. However, the original work for this was performed on canine tissue, in which the COX-1 splice variant retains a COX-like action; in humans, however, the expressed protein has no role in the physiology of prostaglandins. (8,9,10)

Serotoninergic pathway activation

Serotonergic pathways are part of the descending pain system, originating in the brainstem nuclei, hypothalamus, and cortex, and interact with pain afferents in the dorsal horn. Serotonin receptors are present throughout the central nervous system, involved in several functions, including consciousness, mood, memory, and nausea and vomiting, the latter of which are mediated via the 5-HT3-receptor subtype. It has become widely accepted that the activation of descending serotonergic pathways plays a key role in the action of paracetamol, and it has been demonstrated that the anti-nociceptive effects of paracetamol can be partially inhibited by co-administration of 5-HT3-receptor antagonists, interestingly using anti-emetic drugs which are indeed frequently given together with paracetamol in the perioperative period. (10)

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Endocannabinoid enhancement

In the presence of fatty acid amide hydrolase (FAAH), an enzyme found predominantly in the central nervous system, paracetamol (via an intermediary, p-aminophenol, formed in the liver) is conjugated with arachidonic acid to form the active metabolite, Narachidonoylphenolamine (AM404). Analogous to the action of serotonin or norepinephrine reuptake inhibitors, AM404 inhibits the reuptake of the endocannabinoid, anandamide, from synaptic clefts, increasing cannabinoid receptor activation on the post-synaptic membrane. This would explain the experiences of relaxation, tranquillity, and euphoria reported by many paracetamol users, apparently independent of analgesia.

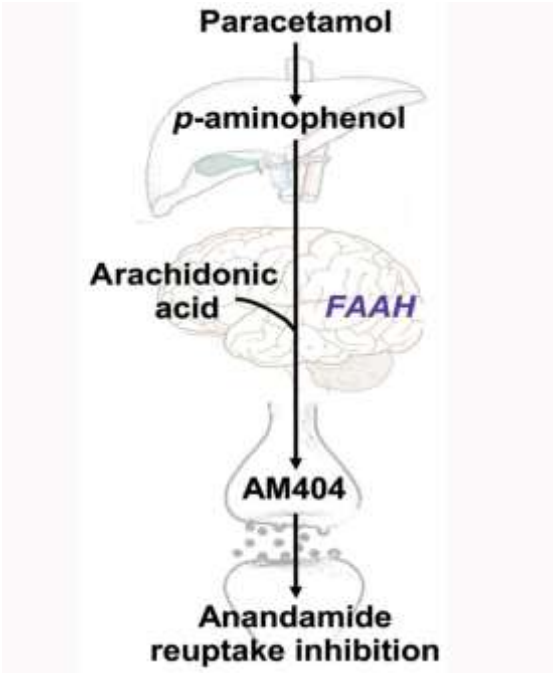

Figure 4: Conversion of paracetamol to AM404, an endocannabinoid reuptake inhibitor.

AM404 appears to be a key player in several pain pathways. Apart from endocannabinoid reuptake inhibition, it has also been shown to activate transient receptor potential vanilloid type 1 (TRPV1) and inhibit cyclooxygenase, NO and tumour necrosis factor-alpha (TNF-α), all involved in acute and chronic pain states. The central production of AM404 would also account for the antipyretic effect of paracetamol, known to be related to inhibition of prostaglandin production in the brain, whilst still without peripheral actions expressed in figure 4.

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Adverse effects of paracetamol

Drug interactions

Interaction with a variety of other drugs may occur, and warrant caution in coadministration. For example, concomitant intake of enzyme-inducing substances, such as carbamazepine, phenytoin, or barbiturates, as well as chronic alcohol excess, may increase NAPQI production and the risk of paracetamol toxicity. Concurrent use with isoniazid also increases the risk of toxicity, though as an enzyme inhibitor, the mechanism is not entirely clear.

Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations in INR values. Increased monitoring of INR should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued as expressed in table 1.

Table 1: Interaction and Effect on Paracetamol

Sr. No.	Interaction Description	Effect on Paracetamol
1	Paracetamol absorption is increased by substances that increase gastric emptying (e.g. metoclopramide)	Increased absorption
2	Paracetamol absorption is decreased by substances that decrease gastric emptying (e.g. anticholinergic agents, opioids)	Decreased absorption
3	Cholestyramine (ion-exchange resin) reduces the absorption of paracetamol if given within 1 h of paracetamol	Reduced absorption
4	Caution with concomitant intake of enzyme-inducing substances, such as carbamazepine, phenytoin, barbiturates, or isoniazid, may increase the risk of paracetamol toxicity	Increased risk of toxicity
5	Probenecid causes an almost two-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A dose reduction should be considered	Reduced clearance
6	Salicylamide (analgesic and antipyretic) may prolong the elimination half-life of paracetamol	Prolonged elimination half-life
7	Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values	Slight INR variations
8	Paracetamol may also increase chloramphenicol concentrations	Increased chloramphenicol concentrations

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Toxicity

Although generally safe, potentially fatal kidney, brain, and liver damage may be caused by acute overdose of paracetamol, and in rare individuals, even after a therapeutic dose, attributable perhaps to the presence of subclinical risk factors such as 'fast-metabolizer' status, glutathione deficiency or both.

However, usage within the therapeutic range, particularly frequent regular use, can also impact on other organ systems, with effects that are less widely acknowledged.

Hepatic

Paracetamol toxicity is the foremost cause of acute liver failure and accounts for most drug overdoses in the UK, USA, Australia, and New Zealand. Paracetamol overdose is the most common and predictable cause, but, in certain individuals, hepatotoxicity may occur with doses within the therapeutic range. This may be secondary to deficiencies in glutathione, because of inadequate nutrition, P450 enzyme induction by chronic alcohol excess, or concomitant use of other drugs.

Paracetamol has, in fact, been shown to be well tolerated in hepatocellular insufficiency and even cirrhosis within the normal recommended dose range, albeit cautiously.

Renal

In general, paracetamol is thought to have only minor effects on renal function, of no clinical relevance in most patients. Rare effects have included acute renal failure, acute tubular necrosis, and interstitial nephritis, but these are usually observed after either acute overdose, chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity; that said, acute tubular necrosis has been observed as an isolated finding in rare cases.

There has been equivocal data regarding whether moderate to long-term use may increase the risk of end-stage renal disease. The mechanism of damage is thought, yet again, to involve the depletion of glutathione—a known anti-oxidant, rendering renal cells particularly sensitive to oxidative damage. Optimizing hydration and nutrition status is therefore of specific relevance in those receiving regular paracetamol.

GI effects

Paracetamol can be associated with non-specific gastrointestinal symptoms, such as nausea and vomiting, dyspepsia, abdominal pain, and bloating. In two large studies in patients with musculoskeletal pain, paracetamol was, in fact, associated with more

'digestive adverse effects' than ibuprofen after 6–14 days of regular oral use, though far less than with diclofenac. These effects, however, were mostly abdominal pain and some nausea, and led to no further complications.

Rarely, cases of acute pancreatitis have been reported, and one study has suggested that acetaminophen may precipitate acute biliary pain and cholestasis, possibly related to inhibition of prostaglandin and alterations in the regulation of the sphincter of Oddi.

Haemodynamic changes

Although also rare, hypotension is a recognized adverse effect, listed in the product information of paracetamol. The limited evidence on the subject would suggest that adults and neonates in a critical care setting, who are either febrile or have pre-existing low blood pressure, may have increased susceptibility to a period of hypotension after either enteral or i.v. paracetamol. Whilst often only modest and brief, a proportion of these hypotensive episodes did require supportive intervention, although no long-term sequelae were reported. In adult patients, the hypotension was associated with increased skin blood flow, consistent with its antipyretic action; these effects were not demonstrated in healthy afebrile volunteers, or in elective surgical patients when given paracetamol perioperatively (11,12).

Conversely, regular use of oral paracetamol has been linked with a raised blood pressure. Whilst much of these data come from retrospective observational studies, results from two small randomized, placebo-controlled crossover trials conducted in patients with known coronary artery disease or treated hypertension suggest that after as little as 2 weeks of paracetamol at submaximal doses of 1 g three times a day, heart rate and blood pressure may show statistically, though perhaps not clinically, significant rises.

Respiratory effects

Although most certainly not an NSAID, paracetamol itself may be causally linked with the development of asthma. There has been mounting evidence since 2000 of an association between asthma and paracetamol usage, so strong that it is thought by some to have contributed to much of the dramatic increase in childhood asthma over the past 30 years. The product information for some commercial preparations of paracetamol itself include in their list of possible adverse effects, difficulty breathing, and bronchospasm in patients having a tendency of analgesic asthma.

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Aside from its role in detoxifying paracetamol in the liver, glutathione is a pulmonary antioxidant, which may limit airway inflammation in asthma. Consistent with findings in animal and in vitro studies that paracetamol may deplete the lung of glutathione, a plethora of, largely epidemiological, data are strongly suggestive that frequent paracetamol usage may be a direct risk factor for wheezing, rhinitis, and asthma morbidity in adults and children. (13)

Cognitive effects

Paracetamol is almost universally acknowledged as the 'non-drowsy' painkiller, and there is no literature to support claims of associated alterations in consciousness in humans. However, there are many anecdotal reports of euphoria or sleepiness (particularly in children and the elderly—groups in which metabolism may be reduced), after paracetamol, even in the absence of pain or pyrexia.(10) As paracetamol is not a known member of any sedative drug group, these experiences are usually dismissed as because of either placebo effect, co-administration with another drug, or pain-relief allowing the user to relax. However, the mechanism of action of paracetamol remains to be determined; pathways gaining credence include the serotonergic and endocannabinoid systems, both of which are intrinsically involved in consciousness and cognitive function. With this in mind, and on the background of some animal studies that have demonstrated some memory impairment after high-dose paracetamol, this may be an avenue for further research.(14)

Haematological/oncological effects

Thrombocytopenia, leukopenia, and neutropenia are listed as very rare (<1/10 000) adverse-effects. Acute thrombocytopenia has also been reported as having been caused by sensitivity to acetaminophen glucuronide. Methemoglobinemia with resulting cyanosis has been observed in the setting of acute overdose.

Looking at more long-term effects, one prospective cohort study of almost 64 000 men and women aged 50–76 yr showed an association between 'high use' of acetaminophen (defined as use on ≥4 days week−1 for ≥4 yr) and an almost two-fold increased risk of incident haematologic malignancies, that was not shared by NSAIDs. These included myeloid neoplasms, non-Hodgkin's lymphoma, and plasma cell disorders, but not chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Somewhat in contrast to this, a protective effect of paracetamol in the development of ovarian cancer has been suggested. A meta-analysis of eight prospective observational studies to include data from over 746 000 patients showed that 'regular use' (definitions varying from use on 4 or more days each month for more than 6 months, to more than once a day for a year) was associated with a statistically significant 30% reduction in the risk of developing ovarian cancer compared with non-use.

The mechanisms of these proposed effects are unknown, and the role of any number of confounding factors cannot be excluded.

Dermatological effects

Pain or a burning sensation may be experienced at the injection site after i.v. administration and 100 ml volume should be infused over 15 min, but whilst uncomfortable, this is short-lived, and does not preclude further administration. The incidence of hypersensitivity is very rare (<1/10 000), reactions ranging from simple skin rash or urticaria to anaphylactic shock.

A range of other, extremely rare, dermatological effects have been reported, from the nonspecific and transitory, such as erythema, flushing, peripheral oedema and pruritus, to severe, life-threatening conditions such as bullous erythema, purpura fulminans, toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), and acute generalized exanthemata's pustulosis.

Headache

Paracetamol is effective in the management of tension-type headache and migraine, though not for cluster headaches. In a meta-analysis of six studies, paracetamol was equianalgesic to low-dose NSAIDs in the treatment of tension-type headache. A combination of paracetamol and caffeine has also been shown to be equivalent to sumatriptan in the acute treatment of migraine.(15)

However, although useful in the treatment of headaches, paracetamol may also contribute to the development of medication overuse headache attributed to excessive ingestion of analgesic agents for relief of other causes of chronic pain, including tension-type headache and migraine. Paracetamol is considered 'overused' when taken on more than 15 days of each month for more than 3 months.

Is paracetamol a sleep-inducing drug?

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As a widely available over-the-counter drug, paracetamol is known to be used for purposes other than for its analgesic and antipyretic actions. This include the use of paracetamol for the induction of sleep, which is based on anecdotal personal experiences (16)

It is logical to reason that such sleep promoting action by paracetamol is a consequence of improvement of the patients' pain experience or is merely a placebo effect. Pilot-controlled clinical trials failed to demonstrate a positive correlation between paracetamol administration and improvement of sleep(17-19).

Considering the thermoregulatory actions of paracetamol are believed to be mediated through inhibition of PGE2 within the hypothalamus, it is thought provoking to reason that paracetamol might have mild sleeping inducing properties, particularly when bearing in mind the fact that PGE2 is known to induce wakefulness(20-22) inhibition of which would promote sleepiness. It is feasible to believe that paracetamol affects common neuronal circuitry mechanisms within the hypothalamus that regulate sleep and body temperature, a paradigm that would be worth further investigation (Reference 23 provides an overview on the CNS neural circuitry and role of prostaglandins in the development of sickness syndrome/behavior that includes fever and increased sleepiness). Indeed, the suprachiasmatic nucleus within the anterior medial zone of the hypothalamus is known to be involved in circadian control of sleep-wake cycle and body temperature.

Final remarks and future considerations on paracetamol

Owing to the fatal hepatotoxicity associated with paracetamol over-dose [24,25], it has been debated whether paracetamol should be withdrawn from the market or to be reclassified. At therapeutic dose paracetamol is a safe drug, but with a narrow therapeutic window, it is easy to accidently or deliberately over-dose. Such debates between clinicians, scientists and drug regulators have been ongoing for some time with the general population rarely being involved in such dialogs. It is predicted that withdrawal of paracetamol from global markets or even its re-classification would not be well received by the general population. As on over-the-counter, most people self-medicate with paracetamol for the management of acute/mild pain and fever. Paracetamol became particularly important during the current global SARS-CoV-2 pandemic as ibuprofen, another over-the-counter analgesic antipyretic drug, was initially contraindicated for these patients [26], a notion that was later rejected [27,28]. Undoubtedly, paracetamol holds a

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unique place as a familiar and widely used analgesic antipyretic drug which for many decades has puzzled pharmacologists in regards to its mechanism of pharmacological actions (Prevailing theories on the mechanisms of pharmacological actions discussed in this review are summarized in Figure 5). From a clinical perspective, withdrawal of paracetamol from the market would leave a void for the management of mild pain and fever whether through physicians' recommendation or patients' own self-medication endeavors and the search for a drug to replace paracetamol may be the way ahead, but equally not necessarily provide a safer alternative. It is worth remembering that a wealth of knowledge on the paracetamol-induced toxicity has accumulated over the many decades of clinical use. Several measures have been put in place to help reduce the paracetamol-induced toxicity that include limits on package size, which has had limited impact [29,30].

Therefore, more steps to help prevent overdosing with paracetamol are needed. Such steps may include helping to provide general awareness on the risks linked to overdosing with paracetamol [31-33]. From a pharmacological perspective, the search for the molecular target for paracetamol continues, which may provide us with a new way to treat pain and fever in the future.

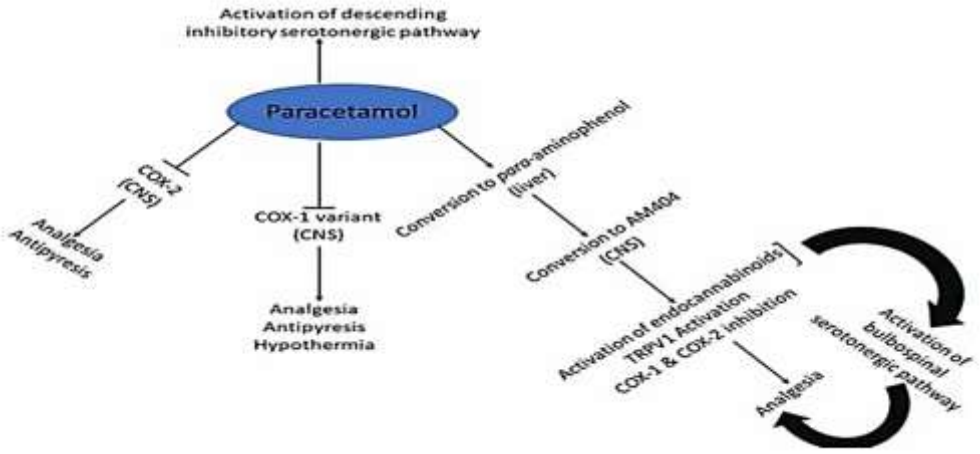

Figure 5. Theories on paracetamol's pharmacological mechanisms.

Conclusion

Paracetamol remains one of the most widely used and accessible over-the-counter analgesics with a favorable safety profile at therapeutic doses, emerging evidence reveals potential adverse effects, particularly with chronic use. These effects include increased risk of gastrointestinal bleeding, elevated blood pressure, and possible cardiovascular,

renal, and respiratory impacts. Additionally, recent studies highlight concerns over in utero exposure and possible long-term effects on development. It is crucial for healthcare providers to carefully weigh the benefits and risks when recommending prolonged paracetamol use, especially in populations vulnerable to its adverse effects. Further research is needed to fully elucidate these risks and refine guidelines for safe usage.

Notes on contributors

Dr. M. K. Gupta, Dr. Girish Kumar Vyas, Dr. Nitin Nama, Me. Rahul Ancheria Supported me a lot for the guidance and writing this paper.

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