RESEARCH PAPER

Paracetamol: Therapeutic uses, Dosage, Administration, Physicochemical properties, Pharmacokinetics, Pharmacodynamic,

Interaction with drugs, and Toxicity

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Abstract
Paracetamol is one of the most widely used drugs worldwide. It was first synthesized from its precursor phenacetin by Harmon Northrop Morse in 1878. It is the first-line of the treatment in the management of mild to moderate pain and fever.Normally the oral dose of paracetamol for adults is 500-1000 mg/4-6 hourly.The most commonly recommended daily dose for children under 12 is 10-15 mg/kg every 4 - 6 hours. Paracetamol is readily absorbed after oral administration, widely distributed and mainly metabolized in the liver by glucuronidation and sulfation pathways. The precise mechanism of action of paracetamol remains not fully understood. The most prevailing theory on the mechanism of its analgesic and antipyretic actions relates to the inhibition of central nervous system cyclooxygenase (COX) enzyme activities, activation of the endocannabinoid systems and vanilloid receptors, and potentiation of the descending inhibitory serotonergic pathway. Paracetamol can interact with some antibiotics, antiviral, antifungal, and anticonvulsant drugs which can increase the hepatotoxicity of paracetamol as a sequence of an increase in the toxic metabolites. NAPQI is a toxic byproduct made when the liver breaks down paracetamol. NAPQI is conjugated with glutathione, a protective antioxidant found in liver cells, to quickly detoxify NAPQI in therapeutic doses. But during situations of overdose, the glutathione stores are depleted, NAPQI starts to accumulate and binds to cellular proteins, dysfunction of mitochondria and finally hepatocellular necrosis.
Keywords: Paracetamol, Acetaminophen, Analgesic, Antipyretic, Hepatotoxicity.

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1. Introduction

Paracetamol is a widely used pain reliever and fever reducer, also known as acetaminophen. Different countries market paracetamol under various names such as Panadol , Tylenol, Crocin, Calpol, and Alvedon. Paracetamol was first synthesized from its precursor phenacetin by Harmon Northrop Morse in 1878, but its use was not widespread initially, due to early reports of a link to methaemoglobinaemia 1.

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 in 1893 2. In 1894, another study showed that paracetamol was comparable to phenacetin in anti-pyretic effect 3, but at that time the paracetamol was not widely used.

In late of 1940s, a biochemists identified paracetamol as a major metabolite of acetanilide in human blood 4, and paracetamol's role in causing methaemoglobinaemia was disputed, and it was regarded as an efficacious analgesic 5.

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 pain and fever 6. Paracetamol sales have increased more than aspirin in numerous countries and acquired popularity quickly, and has become the first line therapeutic agent due to its effectiveness and relatively a good safety specially when used at the recommended doses 7. The global demand for paracetamol is about 200,000 tons per year 8.

2.Medical uses of paracetamol

Paracetamol effectiveness, safety, and availability make it a first-line treatment in the management of mild to moderate pain and fever.It can be used in the treatment of the mild to moderate pain such as headaches, toothaches, myalgia, back pain, joint pain, migraine, and menstrual pain. It is commonly used in postoperative pain, either as a single agent or in combination with other analgesics. The treatment of fever caused by the infection of common cold, influenza, and other viral or bacterial diseases is one of the most common applications of paracetamol 9.

Paracetamol is a safer choice in patients in whom the use of the non-steroidal anti-inflammatory drugs is contraindicated such as in patient with a gastric ulcer, hypersensitivity or bleeding disorder. It is also favoured in both pediatric and geriatric population because of the good safety profile when used properly. Also, paracetamol is often used in combination products with other drugs such as antihistamines, decongestants, and opioids to increase the therapeutic effect in such conditions as cold, cough, and severe pain 10.

3.Paracetamol dosage and routes of administration

3.1. Dosage:

In order to ensure the therapeutic efficacy and to reduce the risk of toxicity like hepatotoxicity related to overdose, appropriate dosage and proper administration is essential. Normally the oral dose of paracetamol for

adults and children 12 years of age and older is 500-1000 mg/4-6 hourly as needed. To promote safety, the highest amount of the drug that is recommended to be used per day is 4 grams per day. But in people with impaired liver, malnutrition, or chronic alcoholic use, the dose must be decreased since these conditions can predispose to toxicity 11.

Regarding the paediatric dosage, the child's weight determines most medicine dosages for children. The dosage must be expressed in milligrams/ kilogram of the child's weight. The most commonly recommended daily dose for children under 12 is 10-15 mg/kg every 4 - 6 hours, with a maximum of 5 doses (50 to 75 mg/kg) in 24 hours to prevent under dose and overdose. It is usually found that in paediatric preparations like syrups, suspensions, and suppositories, which make it easy to adjust the dose based on the child weight 12.

3.2. Routes of administration:

There are various routes of administration of paracetamol. The oral route like paracetamol tablet or paracetamol syrup is the most popular one (Figure-1). It is fast absorbing and can be used with a majority of patients . After administration of a single oral dose, the bioavailability of paracetamol is 0.63 or 0.89, depending on whether the dose ingested was 500mg or 1g respectively11.

Rectal route is useful in paediatrics patients or in conditions where the oral administration is not possible but in this condition the absorption is slower and the bioavailability may be 10–20% lower than that of the oral route, varying in with the volume of the suppository 12, 13.

The intravenous route is usually used in hospitals when its action needs to take place rapidly or when it is impossible to take oral administration of the drug specially in postoperative patients or in vomiting. After the first hour of intake, the plasma concentrations of paracetamol are similar to the oral formulation and the plasma elimination half-lives are identical 14.

Figure-1: Different images shows the oral, rectal, and intravenous route of administrations.

4.Physicochemical properties of paracetamol

Alternate names: Acetaminophen, p-Hydroxyacetanilide, pacetyl aminophenol, N-para hydroxyphenylacetainide

Chemical formula: C8H9NO2

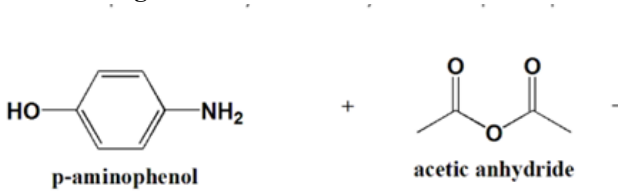
Appearance: White odourless crystalline powder.

Melting point:169-170.5°C

pH: 5.3 to 6.5 at 25°C

Spectroscopy data: Infrared, ultraviolet, nuclear magnetic resonance, fluorescence and mass spectra.

Molecular weight:151.16



Partition coefficient: Pc = 6.237 (octanol: pH 7.2 buffer)

Dissociation constant: pKa = 9.0-9.5

Density:1.293gm/cc

Stability: Dry, pure paracetamol is stable to 45°C.

Solubility: Soluble in water, ethanol, acetone, chloroform, glycerol, and methanol. Slightly soluble in ether. It is insoluble in petroleum ether and benzene 12.

Paracetamol can be synthesized by reaction of p-amiophenol with acetic anhydride 15,16.

Paracetamol can also be administered intravenously and in this condition it gives a quicker onset of activity, and used in acute care conditions to provide immediate peak plasma levels. Rectal administration is commonly applied in pediatric patients. It is associated with slower and lower bioavailability 18.

5.Pharmacokinetics

5.1.Absorption:

When the paracetamol is given orally, it is rapidly absorbed by passive diffusion in the small intestine. The bioavailability is ranging from 70% - 90% and it is a dose-dependent. The maximum plasma concentrations are reached within a half to two hours. Food can retard the rate of absorption, but not affect the overall extent of absorption. It is absorbed mostly in duodenum and upper small intestine 17.

5.2.Distribution:

After paracetamol being absorbed, it is evenly distributed in a majority of body tissues and fluids and and has a volume of distribution of approximately 0.9 L/kg. Paracetamol plasma protein binding is nearly low (5-20%), which implies that a huge percentage of the drug is left unbound and thus pharmacologically remain active 19. Paracetamol can cross the blood-brain barrier, and can exert its central analgesic and antipyretic effects. It can also able to pass through the placenta and is present in breast milk but in a very low concentrations which is considered safe under the normal therapeutic conditions.

The onset time is normally 4-6 hours and for this reason the dosing time is usually 4-6 hours 11.

5.3.Metabolism:

Liver is the most important site for paracetamol metabolism. In healthy individuals, the paracetamol is broken down in three main pathways:

1. Glucuronidation (55%): It conjugation with the glucuronic acid to form a non-toxic metabolites.
2. Sulfation (30%): The other percent of paracetamol is sulphated and then forms sulphate conjugates which are also non-toxic and readily excreted.
3. Minor oxidative pathway (5-10%): It creates NAPQI (N-acetyl-p-benzoquinone imine),a toxic byproduct which is safely neutralized by the liver glutathione which is a naturally occurring antioxidant forming harmless compounds which are excreted in urine 20.

The factors that affecting the metabolism and toxicity of paracetamol can be influenced by several factors like chronic alcoholism, liver disease, malnutrition, and decreases glutathione 21. Paracetamol metabolism is impaired in hepatotoxic doses, and the half-life is prolonged. Sulphate conjugation is saturated and the proportion excreted as mercapturic acid and cysteine conjugates is increased 22.

5.4. Excretion:

In healthy subjects and within 24 hours, 85 to 95% of a therapeutic dose is excreted in the urine as inactive glucuronide and sulfate conjugates, and about 5% appearing as unchanged paracetamol. The plasma half-life is ranges from 2-3 hours and the total body clearance from 4.5 to 5.5 ml/kg/minute. The age has little effect on plasma half-life, but its prolonged in those with liver disease 23.

6.Pharmacodynamics

The mechanism of action of paracetamol is till now not fully understood, but it is mostly act within the central nervous system to bring the analgesic and antipyretic effects .Paracetamol is a moderately lipid-soluble weak organic acid. Its lipid solubility enables it to readily cross the blood-brain barrier and rapidly penetrate cellular membranes24. Products of cyclooxygenase COX-1 and COX-2 enzymes, particularly prostaglandins (PGE2), have been shown to have important roles in the transmission of nociceptive pain. One of the most important processes of paracetamol is inhibition of production PGE2 in the brain. PGE2 are generated by the action of the enzymes cyclooxygenase which is produced during the inflammatory and febrile conditions. Paracetamol blocks these enzymes in central nervous system resulting in the inhibition of the formation of PGE2 which reduces pain signals and lowers a high fever 25.

Recently it was shown that when the paracetamol derived metabolite para-aminophenol, formed in the liver, enters the brain, it conjugates with arachidonic acid through the action of fatty acid amidohydrolase to form N-(4-hydroxyphenyl)-arachidonamide (AM404). AM404 was shown to activate the endocannabinoid system and to also activate the transient receptor potential vanilloid-1 (TRPV-1) channel in the brain and spinal cord , both of which are involved in the modulation of pain signaling and proposed to mediate the analgesic action of paracetamol 26.

Paracetamol also work by increasing activity of the descending serotonergic pathways in the spinal cord, which can helps to block pain signals from reaching the brain, which then reduces pain and lowers the body temperature 27.

7.Interactions between drugs

There is considerable controversy regarding the possible interaction of paracetamol with warfarin in its potential to increase its anticoagulant effects, but no serious adverse drug interactions with therapeutic doses of paracetamol have been confirmed in humans 28.

Combining flucloxacillin antibiotic with a maximum dose of paracetamol carries a rare risk of high-anion gap metabolic acidosis 29. Isoniazide, a tuberculosis drugs can speed up paracetamol breakdown into toxic liver metabolites 30.

Chronic use of alcohol or medicinal products which initiate liver enzymes like zidovudine as antiviral drug, oral ketoconazole an antifungal medication, barbiturates, as a central nervous system depressants, and medications like carbamazepine, phenytoin, phenobarbital, and pirimidone as anticonvulsant drugs can increase the hepatotoxicity of paracetamol as a sequence of an increase in the toxic metabolites 31.

Paracetamol can decrease the clearance of busulfan, and imatinib drugs for cancer treatment, alter paracetamol breakdown, potentially raising drug concentrations higher than intended 32.

8.Adverse reaction to paracetamol

Paracetamol is considered to be safe when it is used within the recommended therapeutic doses, but an overdose is a severe medical condition that can cause severe liver damage. NAPQI is a toxic byproduct made when the liver breaks down paracetamol. NAPQI is conjugated with glutathione, a protective antioxidant found in liver cells, to quickly detoxify NAPQI in therapeutic doses. Nevertheless, during situations of overdose, the glutathione stores are depleted, NAPQI starts to accumulate and binds to cellular proteins, which results in oxidative stress, dysfunction of mitochondria and finally hepatocellular necrosis 33. During the first 24 hours, nausea, vomiting, anorexia, pallor, and abdominal discomfort are common symptoms. Overdosing paracetamol of 140 mg/kg/b.w in children or 7.5g or more in adults can result in cytolytic hepatitis, which can cause irreversible and complete hepatic necrosis. This can lead to acute hepatic failure, metabolic acidosis, hypoglycaemia, bleeding tendencies, and encephalopathy. Patients may go to a multi-organ failure and then death 12.

Acute renal tubular necrosis is occur in 1–2% of patients in paracetamol overdose and most commonly occurs in cases of severe paracetamol induced hepatotoxicity and the possible reasons include the local generation of NAPQI 34.

Other study found that the use of paracetamol has been linked in a small number of cases to thrombocytopenia, pancytopenia, neutropenia, and agranulocytosis 12. Turtle et al 35 study suggest that the long-term paracetamol use increases the risk of developing

hypertension. By contrast, a retrospective observational study by Dawson et al 36 found no impact of paracetamol on blood pressure in 2754 participants with treated hypertension.

Acute allergic responses to paracetamol are very rarely described, but an association between the use of paracetamol in early childhood and the development of atopy was reported 37. In pregnancy, the U.S. Food and Drug Administration (FDA) recommend that paracetamol must be limited to situations where necessary and at the lowest effective dose and for the shortest duration 38. Paracetamol is excreted in breast milk, but the amount ingested by the infant is much lower than paediatric therapeutic doses and rarely associated with clinical effects and must be used at the recommended doses 39.

Conclusions

Paracetamol was first synthesized in 1878 by Morse, and is now probably the most commonly used drug worldwide, It is available both by prescription and over the counter, and used in almost all ages. Oral, rectal, or IV administration is considered as a first line of treatment for mild or moderate pain and pyrexia. Paracetamol is readily absorbed after oral administration, widely distributed and mainly metabolized in the liver. The most prevailing theory on the mechanism of its analgesic and antipyretic actions relates to the inhibition of central nervous system cyclooxygenase (COX) enzyme activities, activation of the endocannabinoid systems and vanilloid receptors, and potentiation of the descending inhibitory serotonergic pathway. It possess a good safety profile except in significant overdose, with a few drug interactions. Overdose of paracetamol leads to liver and kidney damage.

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Conflict of Interests

All authors declare no conflicts of interest.

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