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A REVIEW STUDY ON MODERN PHARMACOLOGY OF PARACETAMOL

Mr. Lalendra Yadav*; Dr. Vishvanayak**

*Department of General Medicine, Teerthanker Mahaveer University,
Moradabad, Uttar Pradesh, INDIA
Email id: yadavlalendra@gmail.com

**Department of General Medicine, Teerthanker Mahaveer University,
Moradabad, Uttar Pradesh, INDIA
Email id: vishvanayak@gmail.com

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ABSTRACT

The analgesic and antipyretic properties of paracetamol are widely utilized throughout the globe. Its effect is comparable to that of NSAIDs, and it is especially similar to COX-2 selective inhibitors. Although paracetamol is a lesser analgesic than NSAIDs or COX-2 selective inhibitors, it is often chosen due to its higher tolerance. Despite its NSAID-like properties, the mechanism of action of paracetamol has been debated, but it is now widely recognized that it inhibits COX-1 and COX-2 by inhibiting their peroxidase activity. This inhibits the production of phenoxyl radicals from a key tyrosine residue required for COX-1 and COX-2 cyclooxygenase activity and prostaglandin (PG) synthesis. When modest amounts of arachidonic acid and peroxides are present, paracetamol inhibits the synthesis of PGs and associated components with selectivity, but it has limited action when significant levels of arachidonic acid and peroxides are present. As a consequence, paracetamol does not suppress the severe inflammation associated with rheumatoid arthritis and acute gout, but it does reduce the milder inflammation associated with tooth extraction and is active in a range of inflammatory tests in experimental animals. COX-2 selectivity seems to be a common feature of paracetamol. The low anti-platelet activity and excellent gastrointestinal tolerability of paracetamol demonstrate its apparent COX-2 selectivity of action. Paracetamol inhibits other peroxidase enzymes, including myeloperoxidase, unlike non-selective NSAIDs and selective COX-2 inhibitors. Paracetamol oxidation and reduced production of halogenating oxidants are involved in myeloperoxidase inhibition.

KEYWORDS: *Diseases, Health, Medicine, Paracetamol, Peroxides.*

1. INTRODUCTION

From birth to death, paracetamol (acetaminophen) is one of the most commonly used non-prescription medications in the world. It is easily accessible and reasonably priced. Paracetamol is a better tolerated analgesic than non-steroidal anti-inflammatory medicines (NSAIDs), but it may be less effective. Because of the link between aspirin and Reye's syndrome, paracetamol became the antipyretic and analgesic of choice in children throughout the 1980s, and it is

currently the standard antipyretic and analgesic in all age groups. Although paracetamol is a valuable and essential medication, the dosage is inconveniently high, and a full dose of 4 g daily necessitates the use of a large number of pills **[1–4].**

He showed that aspirin and other NSAIDs block the production of prostaglandins (PGs), local factors linked with pain, fever, and inflammation, in his Nobel Prize-winning work on the mechanism of action of these medicines. Despite its effects being comparable to those of NSAIDs, paracetamol did not seem to impede PG production. Paracetamol's fundamental pharmacological actions are just now becoming evident, and it is now known to be an inhibitor of PG production in cellular systems under certain circumstances, with apparent selectivity for one of the cyclooxygenase (COX) enzymes, COX-2.

This article provides a review of paracetamol pharmacology, focusing on its mechanism of action and therapeutic effects, with a focus on recent findings. Although its metabolism by peroxidases and the alleged hepatotoxicity of therapeutic dosages are addressed, certain elements of paracetamol's clinical pharmacology, such as its pharmacokinetics, metabolism, and side effects, are not treated in depth. In recent years, new pharmacological effects of paracetamol have been discovered, including its interaction with haem peroxidases such myeloperoxidase, which is addressed in this review. These newly found effects were mostly identified in vitro, but they may lead to new therapeutic applications for an old medication **[5–7].**

1.1.Distribution and chemistry:

The chemical paracetamol has a low molecular mass. Because it is such a weak acid (pKa 9.7), it is virtually unionized at physiological pH levels. Its octanol-to-water partition coefficient is 3.2, which is in the region where passive diffusion across cell membranes is probable. Paracetamol binds to plasma proteins in a minimal amount, with a volume of distribution of approximately 50 L following intravenous administration.

Without binding to tissues, paracetamol spreads throughout the body. This absence of binding means that paracetamol concentrations in vitro may be directly linked with paracetamol concentrations in vivo without any adjustments for tissue absorption or protein binding. After intravenous injection or fast oral absorption, peak plasma concentrations of paracetamol range from about 20 mg/L (130 lM) to 30 mg/L (200 lM), and doses of up to 30 mg/L may be deemed therapeutic. Trough concentrations are on the order of 2 mg/L with a dose of 1 g four times day (13 lM). Paracetamol is a phenol chemically, and like many phenols, it is readily oxidized. This oxidation is crucial to its proposed mode of action as a substrate and inhibitor of COX-1 and COX peroxidase activity. Other haem peroxidases, such as myeloperoxidase, oxidize paracetamol and block it **[8–10].**

1.2. Actions Both Therapeutic and Toxic:

Paracetamol has a lot of similarities with non-selective NSAIDs like ibuprofen, ketoprofen, and naproxen in terms of pharmacology and toxicity, and also shares a lot of similarities with selective COX-2 inhibitors like celecoxib and etoricoxib (Table 1). Paracetamol, on the other hand, has lower analgesic action than both classes of NSAIDs (see the section on paracetamol's clinical analgesic efficacy). The fact that paracetamol, unlike both classes of NSAIDs, has relatively modest antiinflammatory action is a significant distinction.

Paracetamol does not exhibit much of the toxicity associated with therapeutic dosages of NSAIDs, especially that associated with older non-selective NSAIDs. At therapeutic dosages, paracetamol, in particular, does not produce substantial gastrointestinal damage. In aspirin-sensitive asthmatics, paracetamol is a mild precipitant of asthma, but it may increase the incidence of asthma (see the section on bronchoconstriction and asthma). However, paracetamol has a separate and potentially hazardous ‘‘Bronchoconstriction and asthma" section). However, paracetamol has a unique and severe hepatotoxicity that is not observed with NSAIDs (see the ‘‘Adverse effects" section). In contrast to aspirin and salicylate, these kinds of NSAIDs do not cause life-threatening responses when taken in excess.

TABLE 1: SUMMARY OF PHARMACOLOGICAL AND CLINICAL ACTIVITIES OF PARACETAMOL, SELECTIVE COX-2 INHIBITORS AND NON-SELECTIVE NSAIDS

Pharmacological activity	Paracetamol	Selective COX-2 inhibitor	Non-selective NSAID
Analgesia	Active	Active	Active
Antipyresis	Active	Active	Active
Anti-inflammatory	Active in mild inflammation	Active	Active
Anti-platelet	Low activity	Inactive	Active
Damage to stomach and small intestine	Low activity	Low activity	Active
Aspirin-induced asthma	Weakly active	Inactive	Active
Blood pressure	Variable data	Increase	Increase
Renal	Lesser effects than both NSAID classes	Impaired function in stressed kidneys	Impaired function in stressed kidneys
Increased risk of thrombosis	Inactive	Active	Active

Both types of NSAIDs have been linked to a rise in blood pressure, with hypertensive patients experiencing it more than normotensive people. Paracetamol's impact has been researched to a lesser degree, with mixed findings. One noteworthy finding was that paracetamol increased the risk of hypertension in women, despite the possibility of bias owing to the use of paracetamol for painful illnesses. Paracetamol had a smaller impact on blood pressure than NSAIDs in trials on individuals treated with antihypertensive drugs. Blood pressure may rise in certain patient groups, and a recent study found that paracetamol raises blood pressure by about 3 mmHg in individuals with coronary artery disease. It is acceptable to monitor for hypertension in patients who use paracetamol on a regular basis in clinical practice. In critically sick individuals, however, a transient drop in blood pressure has been seen following intravenous administration of paracetamol.

1.3.Paracetamol's clinical analgesic effectiveness Acute pain:

The findings of recent reviews and meta-analyses of paracetamol's analgesic activity and combinations with other analgesics are presented. Single dosages of paracetamol have been shown to have analgesic efficacy in a range of acute pain syndromes; nevertheless, paracetamol

is often less efficacious than NSAIDs. Furthermore, like NSAIDs and selective COX-2 inhibitors, paracetamol has greater analgesic efficacy in acute post-surgical pain than in long-term osteoarthritis pain. Paracetamol, on the other hand, is widely used and increasingly administered intravenously as part of multi-modal analgesic regimens.

1.3.1. Cancer-related discomfort:

Paracetamol is often used in conjunction with opioids to relieve cancer-related pain. It's a must-have medication for hospice patients (IAHPC 2007). Non-opioids such as NSAIDs or paracetamol are given first, followed by combination products for moderate pain containing opioids such as codeine, hydrocodone, or oxycodone, and finally, strong opioids such as morphine or transdermal fentanyl, as needed, until the patient is pain-free, according to the WHO Pain Relief Ladder. This three-step method is low-cost and claims to be 70–90% successful. Paracetamol is often given at step 1 and continued at stages 2 and 3 in Europe and Australia, but only at steps 1 and 2 in North America. Opioids should be given to patients with severe cancer pain right away. Depending on the malignancy and its therapy, a number of different medicines and therapies, such as corticosteroids, antidepressants, epidural dosages of analgesics, and neurolytical methods, may be helpful.

1.3.2. Caffeine and paracetamol:

Caffeine increases the clinical analgesic efficacy of single doses of paracetamol by a modest but statistically significant amount. The enhanced rate of absorption of paracetamol following coffee administration may be the explanation. Caffeine has been shown to have contradictory effects in mice, with caffeine causing both less analgesia and a larger decrease of nitric oxide (NO) production in the spinal cord. Caffeine alone has been shown to decrease PG production by one group, although this finding needs to be confirmed.

1.3.3. Paracetamol's effect on diclofenac-induced COX-2:

Diclofenac at supratherapeutic doses causes the production of COX-2 in a macrophage cell line. Even when t-butyl hydroperoxide is added, a therapeutic concentration of paracetamol (10 lM) inhibits PG production by the macrophage cell line, in contrast to the loss of activity of paracetamol when high levels of peroxides are present in other cellular incubations (see ‘‘Reasons for the apparent COX-2 selectivity of paracetamol" section). However, there was no concentration–response connection in these trials, with comparable levels of inhibition at 10, 100, and 1,000 lM paracetamol. A difficulty with interpreting these findings is that a single wash of the media eliminated very high quantities of diclofenac from the cells. It's possible that residual diclofenac decreased cyclooxygenase activity enough for paracetamol to limit PG synthesis. The first is a more broad investigation of NSAID-induced COX-2 induction. The impact of paracetamol on this generated COX-2 has clinical implications and should be investigated further.

1.3.4. Analgesia:

There's a lot of evidence that paracetamol's analgesic impact is linked to its suppression of PG production and other variables. In animal models, PGs enhance the pain caused by pain mediators such bradykinin, whereas paracetamol decreases bradykinin-induced pain. Second, paracetamol inhibits PG production while also lowering PGE2 concentrations in vivo, resulting

in anti-nociceptive actions in experimental mice. Changes in several neural systems are triggered by inhibition of the synthesis of PGs and related factors (see ‘‘Linkages to other neuronal systems" section), but the data suggest that the primary effect of paracetamol is inhibition of the synthesis of PGs and related factors, with changes in other neural pathways being secondary.

1.3.5. Antipyretic action:

Pyrogens raise PGE2 levels in the cerebral fluid, which causes paresis. Paracetamol prevents this rise. Paracetamol's antipyretic action, like its analgesic effectiveness, seems to be related to COX-2 inhibition, since paracetamol has no effect in COX-2 knockout mice. In addition, while lipopolysaccharide and interleukin-1b do not induce fever in COX-2 knockout animals, they do in COX-1 knockout mice. Because COX-3 is a spicy variation of COX-1, paracetamol's antipyretic effect cannot be attributed to COX-3 suppression. Also, selective COX-2 inhibitors are antipyretic in man.

1.4. Anti-inflammation properties:

The most notable pharmacological difference between paracetamol and COX-2 inhibitors is paracetamol's lack of impact on rheumatoid arthritis inflammation. Paracetamol is not immediately anti-inflammatory in rheumatoid arthritis. Paracetamol, on the other hand, does not reduce PGE2 levels in synovial fluid in rheumatoid arthritis patients, while NSAIDs do. Paracetamol, on the other hand, suppresses inflammation in situations when there is less inflammation, such as after tooth extraction, potentially in osteoarthritis, and in a variety of inflammatory tests in experimental animals. Low amounts of arachidonic acid and/or peroxides may be to blame for paracetamol's suppression of low-grade inflammation; circumstances in which paracetamol is a strong inhibitor of PG production. In large dosages, anti-inflammatory action may be feasible in rheumatoid arthritis, but toxicity precludes this.

1.5. Anti-platelet impact:

Another area of similarity between paracetamol and selective COX-2 inhibitors is that it has minimal anti-platelet action. When administered at high dosages, especially those obtained following intravenous administration, paracetamol does decrease the formation of thromboxane A2 and platelet aggregation at peak concentrations. However, because to paracetamol's short half-life, its action is quickly lost.

Paracetamol has the benefit of non-selective NSAIDs like ibuprofen and naproxen in that it does not interfere with aspirin's antiplatelet action. As a result, paracetamol can be used with low-dose aspirin, a drug that is currently extensively used to avoid heart reinfection. Aspirin's antiplatelet action is not blocked by selective COX-2 inhibitors. The lack of impact of both paracetamol and selective COX-2 inhibitors contributes to paracetamol's apparent COX-2 selectivity.

1.6. Future possibilities and genetic interactions:

There have been few instances of paracetamol or NSAIDs causing genetic interactions. Paracetamol alters the expression of many spinal systems, including increased expression of the insulin-like growth factor-1 receptor, when it causes inflammation and discomfort in rats in a formalin test. Because an antagonist of the insulin-like growth factor receptor blocks paracetamol's analgesic effect, the growth factor seems to play a role in paracetamol's action. Upregulation of phosphorylated (activated) ERK1/2 occurs as well, and it has been related to

paracetamol-induced analgesia. Unfortunately, the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors on these pathways have not been investigated, and it is unclear if the upregulation observed with paracetamol is really due to COX-1 or COX-2 inhibition.

2. DSICUSSION

Analgesic and antipyretic properties of paracetamol are utilized all over the globe. Its effect is comparable to that of NSAIDs, and it is especially similar to COX-2 selective inhibitors. Although paracetamol is a lesser analgesic than NSAIDs or COX-2 selective inhibitors, it is often chosen due to its higher tolerance. Despite its NSAID-like properties, the mechanism of action of paracetamol has been debated, but it is now widely recognized that it inhibits COX-1 and COX-2 by inhibiting their peroxidase activity. This inhibits the production of phenoxyl radicals from a key tyrosine residue required for COX-1 and COX-2 cyclooxygenase activity and prostaglandin (PG) synthesis. When modest amounts of arachidonic acid and peroxides are present, paracetamol inhibits the synthesis of PGs and associated components with selectivity, but it has limited action when significant levels of arachidonic acid and peroxides are present. As a consequence, paracetamol does not suppress the severe inflammation associated with rheumatoid arthritis and acute gout, but it does reduce the milder inflammation associated with tooth extraction and is active in a range of inflammatory tests in experimental animals. COX-2 selectivity seems to be a common feature of paracetamol. The low anti-platelet activity and excellent gastrointestinal tolerability of paracetamol demonstrate its apparent COX-2 selectivity of action. Paracetamol inhibits other peroxidase enzymes, including myeloperoxidase, unlike non-selective NSAIDs and selective COX-2 inhibitors.

3. CONCLUSION

Paracetamol is a well-known medication with extensive prescription and non-prescription usage, and there is little question that it will continue to be an effective analgesic in both acute and chronic pain, both alone and in combination with NSAIDs and opioids. It has a very good safety record and has very few medication interactions. Hepatotoxicity is an obvious issue at high dosages, although the evidence for toxicity at doses up to 4 g/day is debatable. Other analgesics have a worse side-effect profile than paracetamol. The argument over how to strike a balance between acknowledging paracetamol's effectiveness while also limiting its side effects rages on. Paracetamol's mechanism of action is firmly related to PG pathways and their interactions with other pain pathways. New uses for it as an antioxidant are being explored, especially effects linked to myeloperoxidase inhibition.

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