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Review Article

Modern Aspects of the Pharmacology of Acetaminophen: Mechanism of Action, Metabolism, Toxicity

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Abstract

Paracetamol (acetaminophen) is one of the world's most widely used non-prescription medicines from cradle to grave. It is readily available and inexpensive. As an analgesic, paracetamol is better tolerated than the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) although it may be somewhat less efficacious. Paracetamol is used to treat many conditions such as headache, muscle aches, arthritis, backache, toothaches, colds, and fevers. It relieves pain in mild arthritis but has no effect on the underlying inflammation and swelling of the joint. The apparent COX-2 selectivity of action of paracetamol is shown by its poor anti-platelet activity and good gastrointestinal tolerance. Unlike both non-selective NSAIDs and selective COX-2 inhibitors, paracetamol inhibits other peroxidase enzymes including myeloperoxidase. Inhibition of myeloperoxidase involves paracetamol oxidation and concomitant decreased formation of halogenating oxidants (e.g. hypochlorous acid, hypobromous acid) that may be associated with multiple inflammatory pathologies including atherosclerosis and rheumatic diseases.

Introduction

During the 1980s a decline in the use of aspirin due to its association with Reye's syndrome allowed paracetamol to become the antipyretic and analgesic of choice in children [1,2] and it is now the standard antipyretic and analgesic in all age groups. Although a useful and important drug, the dose of paracetamol is inconveniently large and a full dose of 4 g daily requires a large number of tablets to be taken [3]. The mechanism of the basic pharmacological effects of paracetamol is only now becoming clear and it is now recognized to be an inhibitor of PG synthesis in cellular systems under specific conditions and has an apparent selectivity for one of the Cyclooxygenase (COX) enzymes, namely COX-2 [4]. This article is a review of the pharmacology of paracetamol, particularly on its mechanism of action and therapeutic effects, with an emphasis on discoveries that have been made in the past 10 years. Some aspects of the clinical pharmacology of paracetamol, such as its pharmacokinetics, metabolism and adverse effects are not covered in detail although its metabolism by peroxidases and the claimed hepatotoxicity of therapeutic doses are reviewed. New pharmacological actions of paracetamol have been identified in recent years, particularly its interaction with heme peroxidases, such as myeloperoxidase, that is discussed in this review. These recently discovered actions have largely been detected in vitro but may lead to new clinical uses of this old drug [5].

Chemical Compounds

Paracetamol is a low-molecular-mass compound (Figure 1). It is an extremely weak acid (pKa 9.7) and is, therefore, essentially unionised at physiological pH values [6].

Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1,4) pattern. The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen isall conjugated. The presence of two activating groups also makes the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are ortho, para-directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygen and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxideanion.

Synthesis

The original method for production involves the nitration of phenol with sodium nitrate gives a mixture of two isomers, from which they wanted 4-nitrophenol (bp 279 °C) can easily be separated by steam distillation. In this electrophilic aromatic substitution reaction, phenol's oxygen is strongly activating, thus the reaction requires only mild conditions as compared to nitration of benzene itself.

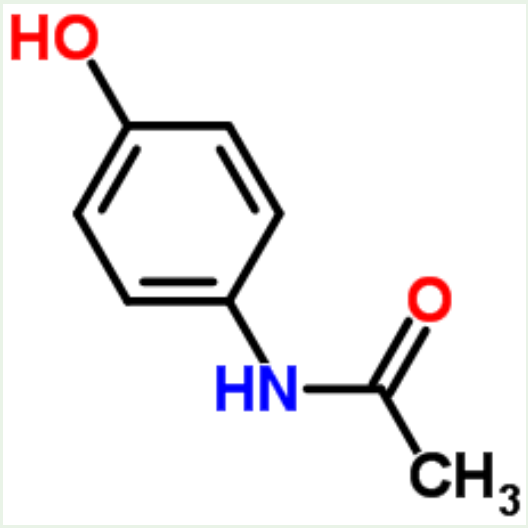

Figure 1: Structure of acetaminophen.

The nitro group is then reduced to an amine, giving 4-aminophenol. Finally, the amine is acetylated with acetic anhydride. Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves (Figure 2).

Therapeutic and Toxicity

Much of the pharmacology and toxicology of paracetamol are similar to those of the non-selective NSAIDs, such as ibuprofen, ketoprofen and naproxen, and it shows particular similarity to the selective COX-2 inhibitors, such as celecoxib and etoricoxib (Table 1). Much of the toxicity of therapeutic doses of NSAIDs, particularly that arising from the older non-selective NSAIDs, is not seen with paracetamol. In particular, paracetamol does not cause significant gastrointestinal toxicity at therapeutic doses [7]. Both classes of NSAIDs have been associated with increase in blood pressure, more so in patients treated for hypertension than normotensive individuals [8]. The effect of paracetamol has been studied to a lesser extent with inconsistent results [9-12]. A notable result is that paracetamol increased the risk of hypertension in women although bias due to taking paracetamol for painful conditions is possible [13].

Acetaminophen Side Effects

Get emergency medical help if you have any of these signs of an allergic reaction to paracetamol: hives; difficulty breathing; swelling of your face, lips, tongue, or throat. Stop using this medication and call your doctor at once if you have a serious side effect such as:

- Low fever with nausea, stomach pain, and loss of appetite;
- Dark urine, clay-colored stools; or
- Jaundice (yellowing of the skin or eyes).

Clinical Analgesic Efficacy of Acetaminophen

The results of some recent reviews and meta-analyses of the analgesic activity of paracetamol and combinations with other analgesics are summarized in Table 2. Single doses of paracetamol show analgesic activity in a variety of acute pain syndromes; however, a common finding is that paracetamol is somewhat less effective than NSAIDs. Furthermore, paracetamol has, like the NSAIDs and selective COX-2 inhibitors, better analgesic activity in acute post-surgical pain than in the long-term pain of osteoarthritis (Table 2). However, paracetamol is used extensively and increasingly given intravenously postoperatively as part of multi-modal analgesia regimens [14,15].

Veterinary Use

Cats

Paracetamol is extremely toxic to cats, which lack the necessary glucuronyl transferase enzymes to break it down safely. Initial symptoms include vomiting, salivation, and discoloration of the tongue and gums. Unlike an overdose in humans, liver damage is rarely the cause of death;

Instead, methemoglobin formation and the production of Heinz bodies in red blood cells inhibit oxygen transport by the blood, causing asphyxiation (methemoglobemia and hemolytic anemia). Treatment with N-acetylcysteine, methylene blue or both is sometimes effective after the ingestion of small doses of paracetamol.

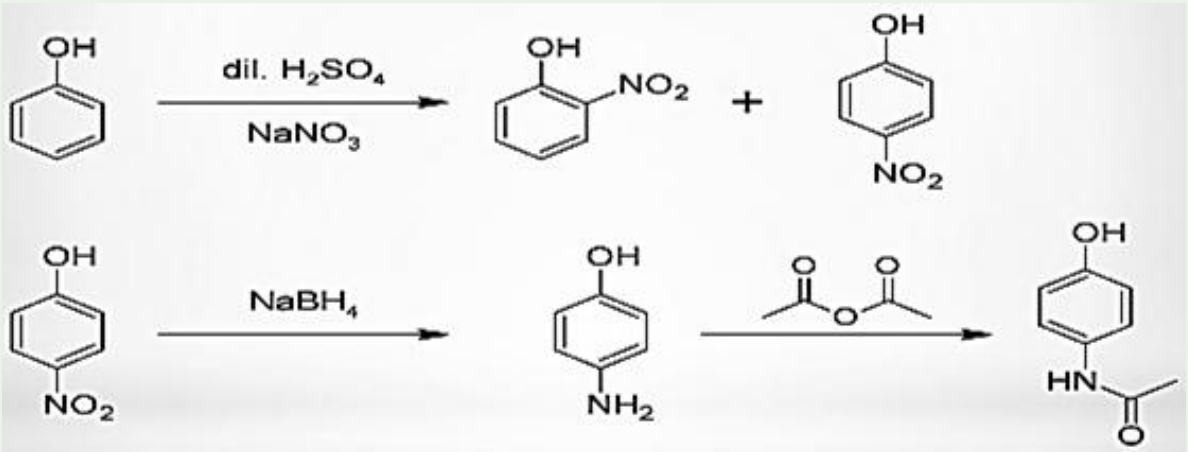

Figure 2: Synthesis of acetaminophen.

Table 1: Pharmacological and clinical activities of acetaminophen.

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

Dogs

Although paracetamol is believed to have no significant anti-inflammatory activity, it has been reported as effective as aspirin in the treatment of musculoskeletal pain in dogs. A paracetamol-codeine product (trade name Pardale-V) licensed for use in dogs is available on veterinary prescription in the UK. It should be administered to dogs only on veterinary advice and with extreme caution. The main effect of toxicity in dogs is liver damage, and GI ulceration has been reported. N-acetylcysteine treatment is efficacious in dogs when administered within two hours of paracetamol ingestion.

Snakes

Paracetamol is also lethal to snakes, and has been suggested as a chemical control program for the invasive brown tree snake (Boigairregularis) in Guam. Doses of 80 mg are inserted into dead mice scattered by helicopter.

Table 2: Clinical analgesic efficacy of acetaminophen.

Pain	Comparison	Number of Clinical trials, number of patients in first group, number of patients in comparator group	Result	References
Osteoarthritis (pain)	P *vs.* placebo	2,193,198	ES[a] = 0.21	[7]
	NSAIDs *vs.* P	11, 824, 814	ES= 0.20	
Osteoarthritis (pain)	P *vs.* NSAIDs	3	ES = 0.33	[13]
Postoperative	P 500mg *vs.* placebo	6, 290, 271	50% pain relief NNT[b] = 3.5, RB[c] = 1.9	[10]
	P 600-650 mg *vs.* placebo	19, 954, 932	50% pain relief NNT = 4.6, RB = 2.4	
	P 975-1000 mg *vs.* placebo	29, 1,903, 1329	50% pain relief NNT = 3.6, RB = 2.7	
Oral surgery pain relief at 6 h	P(<1000 mg) *vs.* placebo	9, 190, 188	50% pain relief NNT = 6, RB = 1.9	[14]
	P(1000mg) *vs.* placebo	6, 487, 690	50% pain relief NNT = 3, RB = 4.2	
Post partum pain	P (500-650 mg) *vs.* placebo	5, 275, 207	Adequate relief NNT = 4, RB = 1.9	[15]
	P(1000 mg) *vs.* placebo	6, 425, 372	Adequate relief NNT = 3, RB = 2.4	
Postoperative including dental	P(800-1000 mg) + codeine (60 mg) *vs.* P (800-1,000 mg)	4, 153, 151	50% pain relief NNT = 6.1, RB = 1.3	[11]
Over 4-6 h	P (600-650 mg) + codeine (60 mg) *vs.* P (600-650 mg)	10, 309, 313	50% pain relief NNT = 8.2, RB = 1.3	
	P(800-1000 mg) + codeine (60 mg) *vs.* placebo	3, 121, 71	50% pain relief NNT = 2.2, RB = 6.3	
	P (600-650 mg) + codeine (60 mg) *vs.* placebo	17, 857, 556	50% pain relief NNT = 3.9, RB = 2.6	
Postoperative including dental Over 4-6 h	P (1000 mg) + oxycodone (10 mg) *vs.* placebo	3, 147, 142	50% pain relief NNT = 1.8, RB = 4.9	[2]
	P(650 mg) + oxycodone (10 mg) *vs.* placebo	10, 680, 363	50% pain relief NNT = 2.7, RB = 3.9	

Acetaminophen Inhibition in Face of Synthesis of Pgs

For many years, the mechanism of action of paracetamol was uncertain. The pharmacological and toxicological properties of paracetamol are consistent with inhibition of the synthesis of PGs from arachidonic acid, the similar actions being particularly noticeable with the selective COX-2 inhibitors (Table 1). However, in broken cell preparations and partially purified COX isoenzymes, only supratherapeutic concentrations of paracetamol inhibit the synthesis of PGs; low concentrations often increase PG synthesis [16,17].

Safety in the Gastrointestinal Tract

PGs are cytoprotective in the stomach and are synthesized by the combination of COX-1 and COX-2 activities and inhibition of both pathways is established as the major cause of the gastrointestinal toxicity of the non-selective NSAIDs. A great attribute of paracetamol is that it has no significant toxicity on the upper gastrointestinal tract [18].

Hepatotoxicity of Acetaminophen

Acetaminophen (APAP) absorption occurs rapidly in the duodenum, owing to its property as a weak acid. If a patient consumes food around the same time of APAP ingestion, there may be a delay in the time of, but not the extent of, drug absorption [10]. Much like concurrent food consumption causing time-delay in APAP absorption, a patient with chronic liver disease is at risk of prolonged drug serum half-life (by an average of 2.0 to 2.5 hours, and up to more than 4 hours), especially if extended-release APAP formulations are consumed. While an overdose of APAP yields peak serum concentrations (10-20 μg/mL) within 4 hours, a patient taking the medication safely will achieve peak concentrations within 1.5 hours, with a half-life of 1.5-3 hours.

Conclusion

Paracetamol is a familiar drug with widespread prescription and non-prescription use and there is little doubt that paracetamol will continue to be a useful analgesic in acute and chronic settings, both alone and in combination with NSAIDs and opioids. It has a remarkable safety record and minimal interactions with other drugs. Hepatotoxicity at excessive doses is a clear problem but the evidence for toxicity at doses up to 4 g/day is questionable. Paracetamol has a superior side-effect profile to other analgesics. The debate regarding the balance between recognizing the efficacy and regulation to limit adverse effects of paracetamol continues. APAP ingestion and subsequent hepatotoxicity is a critical problem that continues to plague individuals across the world, due to the cheap cost of APAP contributing to its being a ubiquitous analgesic and anti-pyretic drug available through consumer pharmacies and as prescription-only medication formulations. Since APAP is responsible for nearly half of the cases of acute liver failure in the United States and remains the leading cause for liver transplantation, continued awareness, education and research should be undertaken. Perhaps due to the attention paid to APAP-induced acute liver failure, survival rates of ~60% are touted as decent when compared to Drug-Induced Liver Injury (DILI) from other substances [19]. New research in detecting biomarkers of injured and necrotic hepatocytes seems promising, especially since it has become increasingly important to identify APAP-induced acute liver injury patients earlier in order to provide lifesaving medical and surgical therapies. While much is currently known about APAP hepatotoxicity regarding its epidemiology, risk factors, pharmacology and toxicology, diagnostics and treatment modalities, there remains a plethora of scientific questions that should be answered in order to improve the understanding of molecular and sub-molecular relationships and pathways that may offer new therapeutics to tackle this curable yet potentially devastating event. The mechanism of action of paracetamol is clearly linked to PG pathways and the consequent interaction with other pain pathways. New indications for its use as an antioxidant are being investigated, particularly effects related to inhibition of myeloperoxidase [20].

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