

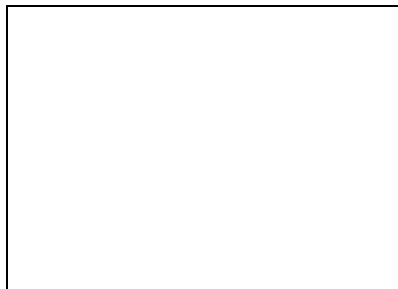
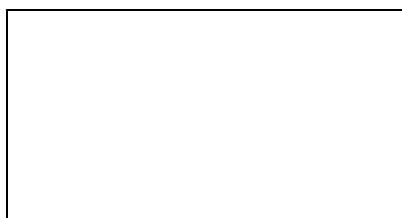
AI Chemistry Group Project

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Drug: **Paracetamol**

-Introduction

Paracetamol (Acetaminophen) is a widely used pain reliever and fever reducer. It is commonly used for the relief of headaches, other minor aches and pains. It is a major ingredient in numerous cold and flu remedies including Panadol and Tylenol. Also, it can also be used in the management of more severe pain such as post surgical pain and providing palliative care in advanced cancer patients. It can relieve pain but has no effect on the underlying inflammation, redness and swelling of the joint. It has painkiller properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better than aspirin in patients in whom excessive gastric acid secretion or prolongation of bleeding time. Available without prescription, it has in recent years increasingly become a common household drug.



IUPAC Name : *N*-(4-hydroxyphenyl)ethanamide /
N-(4-hydroxyphenyl)acetamide

-Lead Compound discovery

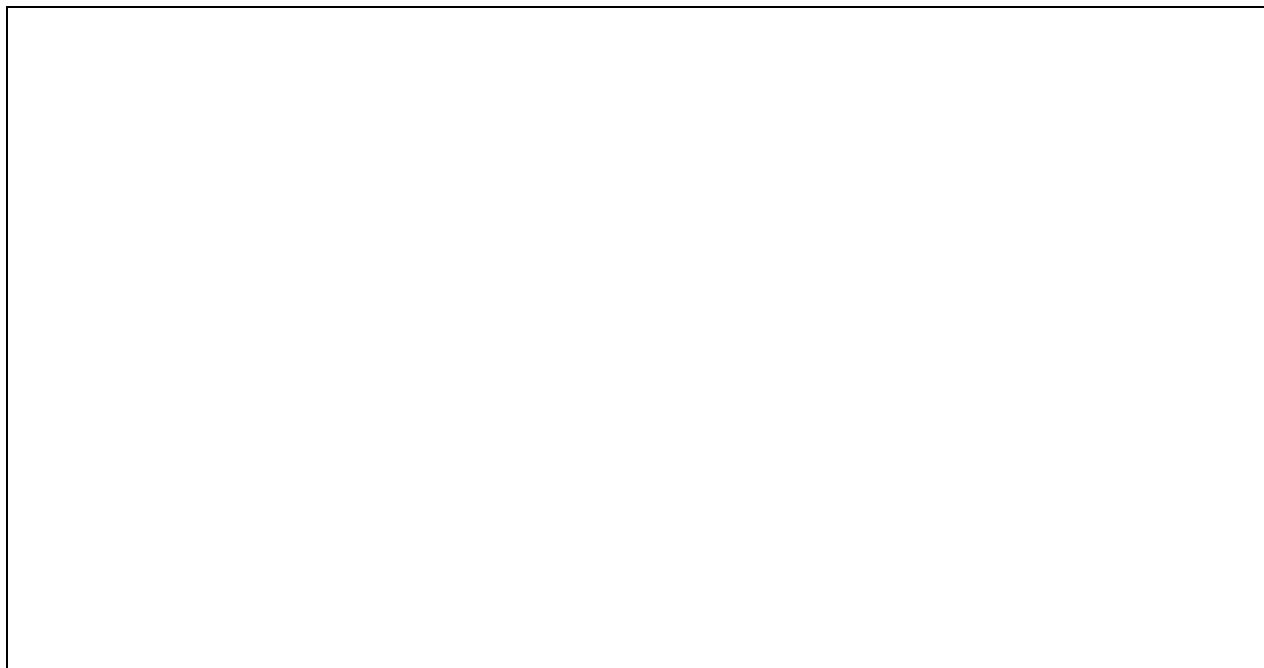
Harmon Northrop Morse had already synthesized paracetamol at Johns Hopkins University via the reduction of *p*-nitrophenol with tin in glacial acetic acid in 1877. In 1893, von Mering published a paper reporting that paracetamol had a slight tendency to produce methemoglobinemia. Paracetamol was then quickly discarded. However in 1947, David Lester and Leon Greenberg found strong evidence that paracetamol was a major metabolite of acetanilide in human blood and large doses of paracetamol given to rats

did not cause methemoglobinemia. They also suggested that methemoglobinemia is produced in humans mainly by another metabolite phenylhydroxylamine. It has been suggested that contamination of paracetamol with 4-aminophenol may be the cause for von Mering's spurious findings. This led to a "rediscovery" of paracetamol.

-Molecular modification

Industrial preparation of paracetamol usually proceeds from nitrobenzene. In the laboratory, paracetamol is easily prepared by nitrating phenol with sodium nitrate, separating the *p*-nitrophenol from the *o*-nitrophenol, and reducing the nitro group with sodium borohydride. The resultant *p*-aminophenol is then acetylated with acetic anhydride. In this reaction, phenol is strongly activating, thus the reaction requires only mild conditions.

Synthesis of paracetamol from phenol:



-Formulation development

Paracetamol is available in a tablet, capsule, liquid suspension, suppository, intravenous, and intramuscular injection.

Combinations with other drugs

- Paracetamol is combined with the opioid codeine, sometimes

referred to as co-codamol. In the United States and Canada, this is marketed under the name of Tylenol #1/2/3/4 which contains 8–10 mg, 15 mg, 30 mg, and 60 mg of codeine respectively. In the UK and in many other countries, this combination is marketed under the names of Tylex CD and Panadeine.

- Paracetamol is also combined with other opioids such as dihydrocodeine, referred to as co-dydramol, oxycodone or hydrocodone which marketed in the U.S. as Percocet and Vicodin respectively.
- Paracetamol is also combined with propoxyphene napsylate which sold under the brand name Darvocet.
- A combination of paracetamol, codeine and the calmative doxylamine succinate is marketed as Syndol or Mersyndol.

Paracetamol toxicity

- **Paracetamol toxicity** is caused by excessive use or overdose of the paracetamol. Mainly causing liver injury, paracetamol toxicity is one of the most common causes of poisoning worldwide.
- Sufferers may initially have nonspecific complaints such as abdominal pain and vomiting. With progressive disease, signs of liver failure may develop. These include low blood sugar, low blood pH, easy bleeding and hepatic encephalopathy. Some will spontaneously resolve but some may result in death.
- Treatment is aimed at removing the paracetamol from the body and replacing it from glutathione. Also, activated charcoal can be used to decrease absorption of paracetamol. The antidote acetylcysteine can help the body regenerate enough glutathione to prevent damage to the liver. A liver transplant is often required if damage to the liver becomes severe. Patients treated early have a good outcome, whereas patients that develop major liver failure typically have a poor outcome.

- Efforts to prevent paracetamol overdose include limiting individual sales of the drug and combining paracetamol with methionine, which is converted into glutathione in the liver.
- recommended doses: 1,000 mg per single dose
4,000 mg per day for adults
2,000 mg per day if drinking alcohol

-Safety test and human trials

- One Sydney hospital alone has recorded 17 cases of liver failure in children from paracetamol since 1985. Five children have died.
- A child in Sydney called Shyann has a viral infection and used paracetamol to relieve the symptoms. Three days later, Shyann's condition had deteriorated. She became semi-unconscious. Also her liver was shutting down. At the time of her death, there was a lot of evidence suggesting that normal recommended doses if used repeatedly could cause liver failure.
- The efficacy of paracetamol by itself in children with fevers has been questioned and a meta-analysis showed it to be less effective than ibuprofen (A kind of anti-inflammatory drug).
- Plasma paracetamol concentrations were measured after oral administration of four healthy volunteers. The formulations were Paramax (paracetamol with metoclopramide), Solpadeine (paracetamol with codeine and caffeine) and Panadol (paracetamol alone). After Solpadeine, concentrations at 15 minutes were significantly higher than after Panadol. Absorption of paracetamol from Paramax tablets did not differ significantly from Solpadeine or Panadol.

- Paracetamol is extremely toxic to cats. Minute portions of a tablet may cause death. Initial symptoms include vomiting, salivation, and discolouration of the tongue and gums.
- It has been reported to be as effective as aspirin in the treatment of musculoskeletal pain in dogs. The main effect of toxicity in dogs is liver damage.
- Paracetamol can also kill snakes. It has been suggested as a chemical control program for the brown tree snake.

-Approval for marketing

- Paracetamol was first marketed in the United States in 1953 which promoted it as being safe to take for children and people.
- The best known brand today for paracetamol in the United States is called Tylenol which was established in 1955 when McNeil Laboratories started selling paracetamol as a pain and fever reliever for children.
- In 1956, paracetamol went on sale in the United Kingdom under the trade name Panadol which is a famous brand called “必理痛” in Hong Kong.
- In 1963, paracetamol was added to the *British Pharmacopoeia* and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.
- In June 2009, a U.S. Food and Drug Administration (FDA) advisory committee recommended that new restrictions should be placed on paracetamol usage in the United States to help protect people from the potential toxic effects. The maximum dosage to be consumed at any given time would be decreased from 1000 mg to 650 mg while combinations of paracetamol and narcotic analgesics would be prohibited.

- On January 13, 2011, the FDA asked manufacturers of combination products containing paracetamol to limit the amount of paracetamol to no more than 325 mg per tablet or capsule and began requiring manufacturers to update the labels of these products to warn of the potential risk for severe liver damage.