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PARACETAMOL: EFFECTS IN HUMAN LIFE AS A SILENT KILLER.

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Abstract:
Paracetamol/acetaminophen is one of the most popular and most commonly used analgesic and antipyretic drugs around the world available without a prescription, both in mono and multi – component preparation. It is a drug of choice in patients that cannot be treated with non- steroidal anti – inflammatory drugs (NSAID), such as people with bronchial asthma , peptic ulcer disease, hemophilia, salicylate – sensitized people, children under 12 yrs of age, pregnant or breast feeding women. It is recommended as a first line treatment of pain associated with osteoarthritis. The mechanism of action is complex and includes the effect of both the peripheral and central antinociception process and "redox" mechanism. Paracetamol is a well tolerated drug and produces few side effects from the gastro intestinal tract, however, despite that, every year, has been a steadily increasing in number of registered cases of paracetamol-induced liver intoxication all over the world.
Keywords: Paracetamol, Acetaminophen, dosage, Acetanilide, Phenacetin, Quinine, drug.

History of Paracetmol:
Paracetamol & acetaminophen are two official names of the same chemical compound derived from its chemical nameN-acetyl-para-aminophenol.Paracetamol (acetaminophen) is a pain reliever and a fever reducer. 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.Paracetamol may also be used for other purposes.

History of paracetamol:
About 100 years ago, the painkilling properties of paracetamol was discovered by accident, when a similar molecule called acetanilide was included to a patient's prescription. In 1893, the white, odourless crystalline compound with a bitter taste that became known as paracetamol was discovered. The pain and fever relieving properties of paracetamol were discovered later**.** Paracetamol was first marketed in the United States in 1953 by Sterling Drug, a global pharmaceutical company in the United States, which promoted it as preferable to aspirin as it was safe to take for children and ulcer patients. Currently, the popular brand for paracetamol in the United States is Tylenol. It was recognized in 1955 when McNeil Laboratories, a pharmaceutical company belonging to the Johnson & Johnson healthcare products group began selling paracetamol as a pain and fever reliever for children, under the brand name 'Tylenol Children's Elixir'. The word "tylenol" was a reduction of para-acetylaminophenol. However, it initially became available on prescription in 1956. At that time, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name 'Panadol', produced by Frederick Stearns & Co, an auxiliary of Sterling Drug Inc. Panadol was initially available only by prescription, for the relief of pain and fever, and then it became as an OTC medicine in 1963. Until the 1970s, issues about paracetamol's safety postponed its prevalent recognition. However, in the 1980s**,** paracetamol sales went beyond those of aspirin in many countries, including the United Kingdom.

Mechanism of action:
Paracetamol is mostly converted to inactive compounds via Phase II metabolism by conjugation with sulfate and glucuronide, with a small portion being oxidized via the cytochrome P450 enzyme system. Cytochromes P450 2E1 (CYP2E1) and 3A4 (CYP3A4) convert paracetamol to a highly reactive intermediary metabolite, N-acetyl-p-benzo-quinone imines (NAPQI).Under normal conditions, NAPQI is detoxified by conjugation with glutathione. In cases

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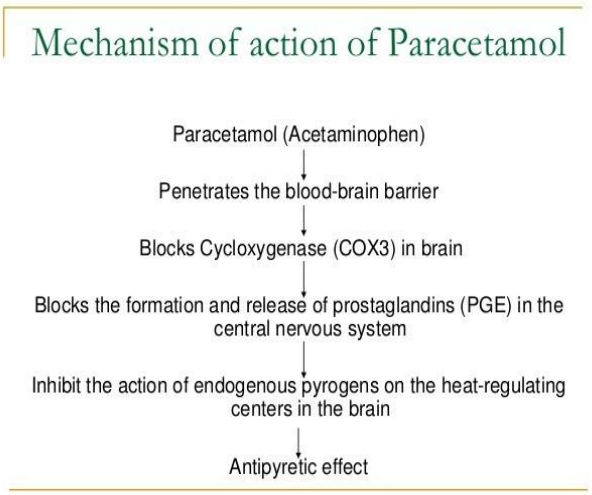
of paracetamol toxicity, the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce NAPQI. As a result, hepatocellular supplies of glutathione become exhausted and NAPQI is free to react with cellular membrane molecules, resulting in widespread hepatocyte damage and death, clinically leading to acute hepatic necrosis. In animal studies, 70% of hepatic glutathione must be depleted before hepatotoxicity occurs.



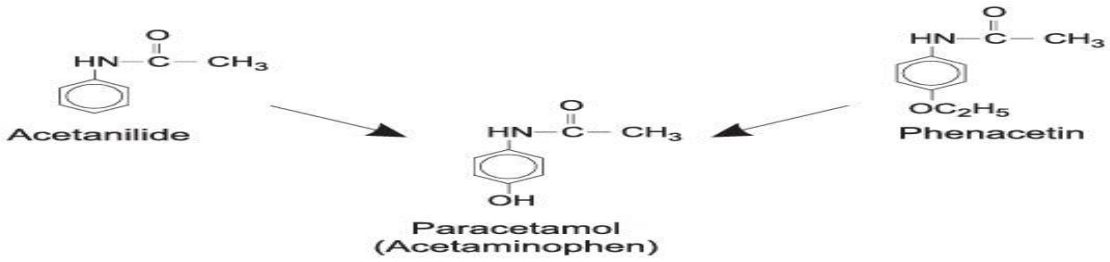


Fig: Chemical structure of analgesics-aniline derivatives

PARACETAMOL DOSAGE GUIDE

	DOSE	FREQUENCY	MAXUMUM DAILY (24 hour) DOSE
ADULTS (including children 12 years and older)	2 x 500mg tablets	Every 4 to 6 hours	4 doses or 8 tablets (4 g) per day
	2 x 665mg tablets	Every 8 hours	3 doses or 6 tablets (4g) per day
CHILDREN (under 12 years)	10-15mg/kg	Every 4 to 6 hours	4 doses or 60mg/kg per day for fever 60-90mg/kg per day for pain

Paracetamol 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).

Rare effects:

- Bloody or black, tarry stools
- bloody or cloudy urine
- fever with or without chills (not present before treatment and not caused by the condition being treated)
- pain in the lower back and/or side (severe and/or sharp)
- pinpoint red spots on the skin
- skin rash, hives, or itching sores, ulcers, or white spots on the lips or in the mouth
- sudden decrease in the amount of urine
- unusual bleeding or bruising
- Unusual tiredness or weakness & yellow eyes or skin.

paracetamol toxicity:

- Hepatotoxicity result not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI).NAPQI decreases the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure.
- Treatment is aimed at removing the paracetamol from the body and restoring glutathione.
- Activated charcoal can be used to decrease absorption of paracetamol if the person presents for treatment soon after the overdose; the antidote acetylcystene act as Prolonged use of acetaminophen (4 or more times per week for four years or more) nearly doubled the risk of certain cancers involving blood cells. a precursor for glutathione, helping the body regenerate enough to prevent damage to the liver.
- A liver transplant is often required if damage to the liver become severe.
- Paracetamol is considered by the doctor to be safer than aspirin, which can cause stomach bleeds, and ibuprofen, which has been linked to heart attacks and strokes.

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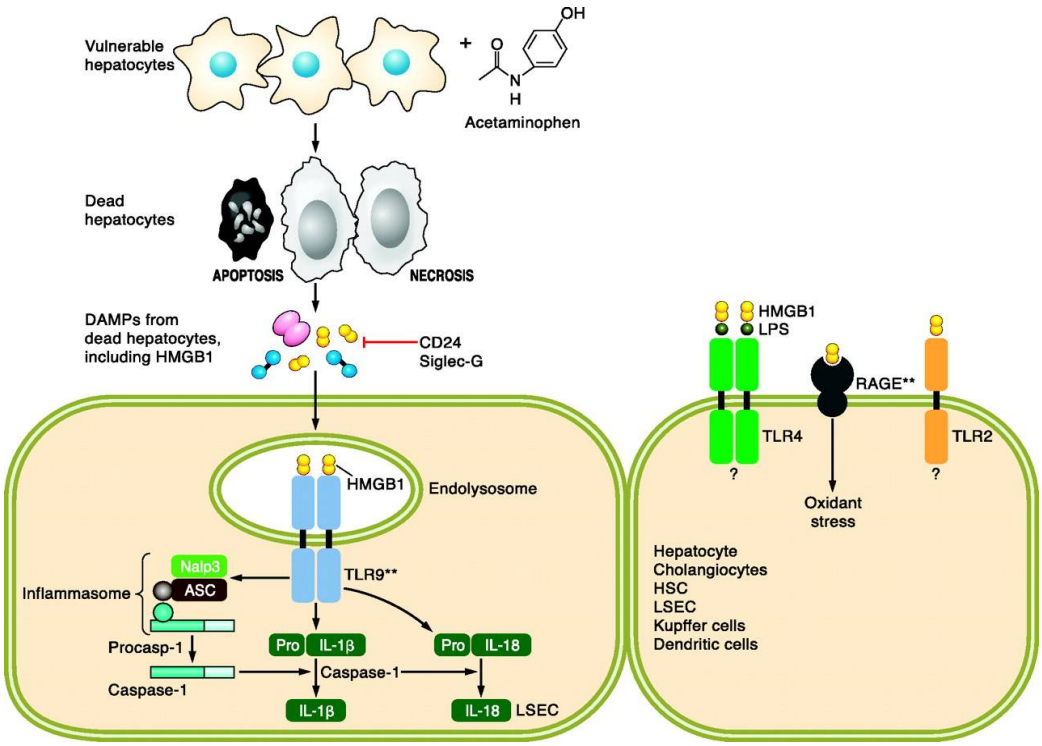

(Fig; hepatotoxicity induced by paracetamol)

Conclusion:

Paracetamol monotherapy is efficient, well tolerated by the majority of patients and safe, on condition that the drug is administered at therapeutic doses. We should, however, bear in mind that paracetamol overuse even at therapeutic doses in some situations like improper slimming, smoking, alcohol abuse or ingestion of other medicines may cause severe hepatic damage or death. It is very important to the patients to be warned by the doctors or pharmacist about the risk connected with the ingestion and particularly with the over dosage of drug. A long term use of high dose carries the risk of adverse reaction typical for COX-2 inhibitors such as hypertension, heart infarction or renal failure. Intravenously administered paracetamol at high doses inhibits platelet aggregation, which is very important in treatments of patients with disorders of hemostasis. It should be remembered that despite the fact that paracetamol has a wide clinical application it is not a drug devoid of side effects. The balance of benefit and losses should be made before deciding to take treatment with paracetamol.

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