POISON CONTROL

VOLUME 7

POISONOUS EFFECTS OF PARACETAMOL OVERDOSE

INTRODUCTION

Paracetamol also known as acetaminophen is the most widely used over-the-counter analgesic in the world. It is also one of the most widely used medications in the world. Paracetamol is very effective in treating mild to moderate pain, pyrexia (fever) and inflammation. Paracetamol poisoning is caused by excessive use of the medication. Because of how effective and popular paracetamol is, it is easily abused. Paracetamol is generally considered as safe when taken as directed but can be extremely hazardous when misused often due to its toxic effects on the liver. Paracetamol is involved in a high number of accidental paediatric exposures and wilful self-poisoning instances. In this article, we will explore the importance of understanding paracetamol poison control emphasizing on the poisonous effects of paracetamol when abused.

HOW CAN PARACETAMOL BE OVERDOSED?

Paracetamol is a widely available OTC (over-the-counter) analgesic and antipyretic agent that is found in brand names like Emzor®, Panadol® and cold/flu medications like Flucor day® and Procold®.

Paracetamol poisoning comes as a result of paracetamol overdose. Paracetamol overdose is the excessive intake of paracetamol over the recommended dose. The recommended dose of paracetamol for adults is 4 g or 75 mg/kg in 24 hours while for children is 15 mg/kg per dose with a maximum of 60 mg/kg in 24 hours. In adults, toxicity is uncommon if less than 4 g is ingested within 24 hours.

Generally, the toxic dose of paracetamol is highly variable.

Chronic paracetamol poisoning result from the long-term overuse or misuse of paracetamol in doses higher than the recommended 4 g daily amount.

Paracetamol poisoning can occur as an attempt to commit suicide. A single acute overdose is defined as consuming more than 4 g or greater than 75 mg/kg in less than an hour. This is usually with the intention of self harm.

Paracetamol overdose can also occur unintentionally when multiple products that contain paracetamol are consumed simultaneously. For example, cold and flu medications, prescription pain killers and combination of analgesics containing paracetamol.

In rare cases, paracetamol toxicity can result from normal use and dose in some individuals. This may be due to individual differences in the metabolism of paracetamol.

The severity of paracetamol toxicity varies depending on the dose and whether appropriate treatment is received.

TYPES OF PARACETAMOL POISONING

1. Chronic Paracetamol Poisoning
2. Acute Paracetamol Poisoning
3. Staggered Overdose
4. Repeated Supratherapeutic Paracetamol Ingestion

Chronic Paracetamol Poisoning: This occurs as a result of long-term paracetamol abuse and misuse. Ingestion of higher than recommended 4 g daily dose of paracetamol, in an adult, over a long period of time is termed chronic paracetamol overdose. Abuse/misuse of paracetamol could also be ingesting paracetamol more frequently than prescribed to handle pain or fever that could go away without taking any analgesic. Practicing this dangerous drug behaviour for a long period of time could lead to acute manifestations of chronic poisoning.

Acute Paracetamol Poisoning: Acute paracetamol poisoning happens when an adult consumes more than 4 g or greater than 75 mg/kg in less than an hour.

Staggered Overdose is the ingestion of repeated doses of paracetamol over a period of more than an hour, with the goal of self harm.

Repeated Supratherapeutic Paracetamol Ingestion: Consumption of extra doses of paracetamol, which is commonly practiced, with the goal of treating pain or fever. This can happen over a long period of time.

HOW DOES PARACETAMOL WORK AND WHEN DOES POISONING OCCUR?

Paracetamol works by inhibiting the production of prostaglandins in the central nervous system. Prostaglandins are chemicals in the body that cause inflammation and pain. When compared to other NSAIDs like diclofenac and ibuprofen, paracetamol has a less significant anti-inflammatory effect but is highly preferred for its mild side effect profile and lack of stomach irritation.

After paracetamol activity in the body, it is being broken down for excretion in the liver in a process known as metabolism. This metabolism is done through several pathways using different enzymes (chemicals that aid metabolism). When paracetamol is taken in normal therapeutic doses, it is mostly converted to non-toxic metabolites but 5% of paracetamol is converted to a highly reactive and poisonous metabolite called N-acetyl-p-benzoquinone imine (NAPQI). This poisonous metabolite is detoxified by another chemical called glutathione to form non- toxic metabolites.

In cases of paracetamol overdose, the demand for glutathione to detoxify this poisonous chemical NAPQI is higher than the liver supply of glutathione. This leads to build up of the toxic NAPQI resulting to a widespread of liver cells damage and death.

RISK FACTORS OF PARACETAMOL POISONING

Having any of these risk factors significantly increases the likelihood of paracetamol poisoning:

- Alcohol consumption
- Fasting
- Existing liver conditions
- Malnutrition
- Chronic use of paracetamol
- Concomitant use with other drugs like isoniazid, carbamazepine, phenytoin, and barbiturates (phenobarbital, barbital, etc.)

PHASES OF PARACETAMOL POISONING WITH THEIR ACCOMPANYING SIGNS AND SYMPTOMS

The signs and symptoms of paracetamol poisoning typically occur in different stages.

Phase 1: Initial phase (0-24 hours)

The first phase begins within the first hours of overdose and lasts 24 hours. Symptoms may be minimal or non-existent.

- Nausea
- Vomiting
- Pale appearance
- Loss of appetite
- Sweating
- General weak/sick feeling
- Liver enzymes may start to increase, but this may not be apparent to the patient.
- In some severe cases of massive overdose, symptoms of metabolic acidosis (accelerated heartbeat, confusion,) and coma is observed in the first stage.

Phase 2: Progression to Severe Toxicity (24-72 hours)

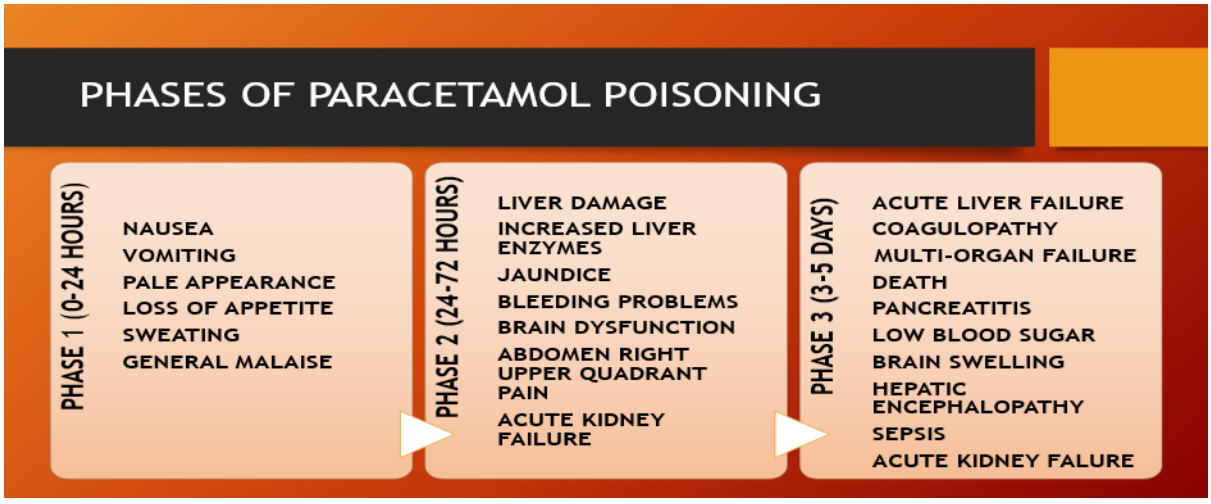
Symptoms become more noticeable as damage happens to liver cells:

- Liver damage with increased level of liver enzymes (AST, ALT, Bilirubin) in the blood.
- Jaundice (yellowing of eyes and skin) may develop.
- Bleeding problems due to impaired clotting
- Confusion, and other signs of hepatic encephalopathy (brain dysfunction as a result of liver failure).
- Right upper quadrant pain in abdomen
- Acute kidney failure in cases where toxic NAPQI is produced more in the kidneys

Phase 3: Severe Liver Failure and Multisystem Organ Damage (3 -5 days):

- Acute Liver Failure**:** The liver can fail completely, causing confusion, agitation, and coma (hepatic encephalopathy).
- Coagulopathy (bleeding disorders) can occur due to impaired liver function.
- Multi-organ failure (liver, kidneys, heart might stop working)
- Death**:** In the most severe cases, multi-organ failure can result to death if the overdose is not treated quickly.
- Pancreatitis
- Low blood sugar
- Brain swelling
- Sepsis
- Acute Kidney failure
- Hepatic encephalopathy

The severity and recovery from paracetamol toxicity depends on the toxic dose and if appropriate treatment is received on time.



DIAGNOSIS OF PARACETAMOL POISONING

Paracetamol overdose can be diagnosed by obtaining information on the patient's medication history and it is confirmed with the blood level of paracetamol at particular intervals after the medicine was taken. After a typical dose of paracetamol,

the concentration in serum is below 30mg/L or 200 mol/L. In overdose patients, levels of 30–300 mg/L (200–2000 mol/L) are common.

An increase in the liver enzymes can also be used to confirm paracetamol overdose.

TREATMENT OF PARACETAMOL TOXICITY

Gastrointestinal Decontamination

This is a critical emergency procedure done to remove medicine from the intestinal tract. The most effective gastrointestinal decontamination procedure for paracetamol poisoning is the use of activated charcoal. It is best administered within **30 minutes** to **two hours** of ingestion of overdose. Gastric lavage, better known as stomach pumping, can be considered if the amount ingested is potentially life-threatening and the procedure can be performed within **60 minutes of ingestion**. Children under six years of age do not need activated charcoal or gastric lavage as liver injury is extremely rare after accidental ingestion of paracetamol overdose.

Acetylcysteine

Acetylcysteine or *N*-acetylcysteine or NAC replenishes the body levels of antioxidant, glutathione, when administered in cases of paracetamol toxicity. Glutathione neutralizes the toxic NAPQI metabolite so that it does not damage the organ cells and is safely excreted. Acetylcysteine has been shown to be a more effective antidote, particularly in patients presenting **greater than 8 hours post-ingestion** and for those who present with liver failure symptoms. Acetylcysteine significantly reduces the risk of serious hepatotoxicity and guarantees survival.

Liver Transplant

If paracetamol overdose patient does not receive immediate help, irreversible liver damage is likely to occur and the patient might need a liver transplant. The patient should be hospitalized to receive intensive care and prevent further disease progression.

Treatment of Symptoms and Monitoring of Liver Enzymes

Symptoms of paracetamol poisoning like metabolic acidosis, coagulation defects, low blood sugar, sepsis, hepatic encephalopathy and so on should be treated if the symptoms do not regress after immediate treatment of paracetamol overdose with Acetylcysteine, Gastric lavage, or Activated charcoal. The liver enzymes should also be continuously monitored to check disease progression or recovery.

Prompt recognition of symptoms and treatment with acetylcysteine is highly important as delay could lead to irreversible complications as stated above and death.

TIPS FOR PREVENTION OF PARACETAMOL POISONING

1) **Take proper dosage as Prescribed:** Use paracetamol as prescribed by health professional. Do not take more than the dosage prescribed at a time.

Don’t take the next dose earlier than prescribed, and do not take for a longer period than prescribed. Don’t abuse paracetamol when you don’t need it, for example, some pains and fever might not need treatment with analgesic. Avoid consuming paracetamol until it’s absolutely necessary.

2) **Don’t take paracetamol with other drugs like, isoniazid, ketoconazole, leflunomide, carbamazepine, phenytoin, barbiturates (phenobarbital, barbital, etc.) and alcohol:** These drugs make use of the same enzymes for metabolism as paracetamol so this can lead to a competitive inhibition of their metabolism. This can deplete the glutathione stores in the body, resulting in excess of the toxic chemical, NAPQI, in the liver. Avoid taking any of these drugs with paracetamol. Consult with a medical doctor or pharmacist if you need to combine any of these drugs with paracetamol. You should inform your doctor or pharmacists of the medications you are already on before more is prescribed.
3) **Adequate Diet and Nutrition:** Malnourishment could lead to a deficiency of glutathione. Malnutrition and fasting puts you at a higher risk of liver injury following paracetamol overdose. Ensure that you are on an adequate diet and you have not fasted for a long time before taking paracetamol.
4) **Precaution in Chronic Sicknesses/Disorders**: Precaution should be taken in chronically ill patients with reduced nutritional intake**.** These patients might have lower glutathione levels increasing their risk for liver damage.
5) **Practice Safe Disposal and Storage of Medication:** Old medicines no longer in use should be properly disposed either by flushing, returning to pharmacy etc., to prevent accidental ingestion of paracetamol overdose by unsuspecting adults or children.
6) **Label Dispensing Containers Properly:** The bottles or envelops containing paracetamol should be labelled clearly and legibly to avoid ingestion by a person with bad eye sight. Also, the labels should be easily recognised by touch to assist the visually impaired.
7) **Precaution in Alcohol-use-disorder:** Chronic consumption of alcohol depletes glutathione levels, hence; an alcoholic is significantly exposed to liver damage following paracetamol overuse. Caution should be employed in consuming paracetamol if you are an alcoholic or recovering alcoholic. Paracetamol should be taken in safe doses and only when prescribed by medical practitioner.
8) **Precaution in Patients with Pre-existing Liver conditions:** Patients with already existing liver conditions need to take extra care with paracetamol. The dose might need to be adjusted to safer doses before administration.

CONCLUSION

Paracetamol is a widely available and effective drug. But as with all drugs it should be handled with caution as all drugs could be poisonous when taken without proper medical recommendation. Paracetamol, as seen in this article, could be a potentially

hazardous drug when not stored properly; disposed wrongly; and when overdosed intentionally or unintentionally. Paracetamol poisoning arises as a result of overdose and could be deadly when not treated promptly. Safe handling and consumption of paracetamol should be practiced by all to prevent the toxic effects paracetamol poisoning.

REFERENCES

https://www.researchgate.net/publication/361164614_Effects_and_treatments_of_paracetamol_toxicity

https://www.omnicalculator.com/health/paracetamol-dosage

Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action - PMC

https://en.wikipedia.org/wiki/paracetamol-poisoning

https://www.lybrate.com/medicine/procold-tablet

Paracetamol Interactions Checker - Drugs.chttps://www.drugs.com/drug-interactions/acetaminophen,paracetamol.html#:~:text=There%20are%20115%20drugs%20known%20to%20interact%20withom

https://greenbook.nafdac.gov.ng/products/details/5057