A REVIEW ON ACETAMINOPHEN TOXICITY, THE JOURNEY SO FAR

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ABSTRACT
Acetaminophen being one of the commonest drugs taken over the counter may be doing more harm than good to its beneficiaries. It is actually used to relieve mild to moderate pain from headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, and reactions to vaccinations, and to reduce fever. Acetaminophen may also be used to relieve the pain of osteoarthritis. However, studies have shown that, excessive use or overdose of the analgesic drug paracetamol (called acetaminophen in North America) leads to toxicities. Mainly causing liver injury, paracetamol toxicity is one of the most common causes of poisoning worldwide. This study found that, in the United States and the United Kingdom it is the most common cause of acute liver failure. Thus, this paper review focuses on the hepatotoxicity, (damage to the liver) of paracetamol which results not from the drug itself, but from one of its metabolites; N-acetyl-p-benzoquinoneimine (NAPQI) (also known as N-acetylimidooquinone). NAPQI depletes the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure. It has been reported that following a therapeutic dose, it is mostly converted to nontoxic metabolites 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 and 3A4 convert approximately 5% of paracetamol to a highly reactive intermediary metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which under normal conditions, is detoxified by conjugation with glutathione to form cysteine and mercapturic acid conjugates, but in cases of paracetamol overdose (due to alcoholism and unconscious intake of drugs containing acetaminophen), the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce the toxic intermediate NAPQI. As a result, hepatocellular supplies of glutathione become depleted, as the demand for glutathione is higher than its regeneration. NAPQI therefore remains in its toxic form in the liver and reacts with cellular membrane molecules, resulting in widespread hepatoctytedamage and death, leading to acute hepatic necrosis. Based on these findings, the strategies for reducing harm done by acetaminophen overdoses is first by increasing awareness and also selling paracetamol pre-combined in tablets either with an emetic or an antidote e.g. Calcitriol, Paradote and L-5-oxo-pyrrolidine-2-paracetamol carboxylate etc.

Introduction
Acetaminophen whose common names are; Paracetamol, Tylenol, Panadol, is a crystalline compound (C8H9NO2) used in medicine to relieve mild to moderate pain from headaches, muscle aches, menstrual periods, colds and sore throats, toothaches, backaches, and reactions to vaccinations and to reduce fever (Pocket Medical Dictionary). Acetaminophen may also be used to relieve the pain of osteoarthritis (arthritis caused by the breakdown of the lining of the joints). Acetaminophen is in a class of medications called analgesics (pain relievers) and antipyretics (fever reducers). Unfortunately, because of its analgesic activities acetaminophen happens to be one the most abused and misused drugs in the world; where some people take it to enhance their physical activities, to write and read books, even to stay awake watching movies (Bertram, 2001). It works by changing the way the body senses pain and by cooling the body. Acetaminophen may also be used in combination with aspirin and caffeine to relieve the pain associated with migraine headache. This medication is sometimes prescribed for other uses.

![Fig 1: Structure of Paracetamol](image)

**Paracetamol toxicity** is caused by excessive use or overdose of the analgesic drug paracetamol. Mainly causing liver injury, paracetamol toxicity is one of the most common causes of poisoning worldwide. In the United States and the United Kingdom it is the most common cause of acute liver failure (Ryder et al., 2001; Larson et al., 2005). Many individuals with paracetamol toxicity may have no symptoms at all in the first 24 hours following overdose. Others may initially have nonspecific complaints such as vague abdominal pain and nausea. 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, although untreated cases may result in death.

Damage to the liver, or hepatotoxicity, results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI) (also known as N-acetylimidoquinone) (Larson et al., 2005) NAPQI depletes the liver’s natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure (Ryder et al., 2001; Larson et al., 2005).
Fig 2: Main pathways of paracetamol metabolism the pathway leading to NAPQI is shown in red.

Fig. 2: Phase II Acetaminophen metabolism
When taken in normal therapeutic doses, paracetamol has been shown to be safe (Heard, 2008). Following a therapeutic dose, it is mostly converted to nontoxic metabolites via Phase II metabolism by conjugation with sulfate and glucuronide, with a small portion being oxidized via the cytochrome P450 enzyme system (Larson et al., 2005). Cytochromes P450 2E1 and 3A4 convert approximately 5% of paracetamol to a highly reactive intermediary metabolite, N-acetyl-\(p\)-benzoquinoneimine (NAPQI) (Corcoran et al., 1980; Rumbeiha et al., 1995; Richardson, 2000; Heard, 2008). Under normal conditions, NAPQI is detoxified by conjugation with glutathione to form cysteine and mercapturic acid conjugates (Mitchell et al., 1973).

In cases of paracetamol overdose, 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 depleted, as the demand for glutathione is higher than its regeneration (Mitchell et al., 1973). NAPQI therefore remains in its toxic form in the liver and reacts with cellular membrane molecules, resulting in widespread hepatocyte damage and death, leading to acute hepatic necrosis (Dai and Cederbaum, 1995).

**Risk factors**

A number of factors can potentially increase the risk of developing paracetamol toxicity. Chronic excessive alcohol consumption can induce CYP2E1, thus increasing the potential toxicity of paracetamol. In one study of patients with liver injury, 64% reported alcohol intakes of greater than 80ml a day, while 35% took 60ml a day or less (Zimmerman and Maddrey, 1995). Whether chronic alcoholism should be considered a risk factor has been debated by some clinical toxicologists (Dargan and Jones, 2002). For chronic alcohol users, acute alcohol ingestion at the time of a paracetamol overdose may have a protective effect (Dargan and Jones, 2002; Buckler and Srinivivasan, 2002). For non-chronic alcohol users, acute alcohol consumption had no protective effect.

Fasting is a risk factor, possibly because of depletion of hepatic glutathione reserves (Daly et al., 2008). The concomitant use of the CYP2E1 inhibitor isoniazid increases the risk of hepatotoxicity, though whether 2E1 induction is related to the hepatotoxicity in this case is unclear (Crippin, 1993; Nolan et al., 1994). Concomitant uses of other drugs that induce CYP enzymes, such as antiepileptics including carbamazepine, phenytoin, and barbiturates, have also been reported as risk factors (Bray et al., 1992).

**Treatment**

Treatment is aimed at removing the paracetamol from the body and replacing glutathione. Activated charcoal can be used to decrease absorption of paracetamol if the patient presents for treatment soon after the overdose; the antidote acetylcysteine acts as a precursor for glutathione, helping the body regenerate enough to prevent damage to the liver (Roth et al., 1999).
Acetylcysteine, also called N-acetylcysteine or NAC, works to reduce paracetamol toxicity by replenishing body stores of the antioxidant glutathione. Glutathione reacts with the toxic NAPQI metabolite so that it does not damage cells and can be safely excreted (Piperno and Berssenbruega, 1976). Cysteamine and methionine have also been used to prevent hepatotoxicity (Mant et al., 1984; Brok et al., 2006). Although studies show that both are associated with more adverse effects than acetylcysteine (Daly et al., 2008). Additionally, acetylcysteine has been shown to be a more effective antidote, particularly in patients presenting greater than 8 hours post-ingestion (Alsalim, and Fadel, 2003). Oral acetylcysteine is given as a 140 mg/kg loading dose followed by 70 mg/kg every four hours for 17 more doses, and if the patient vomits within 1 hour of dose, the dose must be repeated (Woo OF et al., 2000).

Intravenous acetylcysteine is given as a continuous infusion over 20 hours for a total dose 300 mg/kg. Recommended administration involves infusion of a 150 mg/kg loading dose over 15 to 60 minutes, followed by a 50 mg/kg infusion over four hours; the last 100 mg/kg are infused over the remaining 16 hours of the protocol (Daly et al., 2008). Liver transplant is recommended in patients who are expected to die.

Recommendations

One strategy for reducing harm done by acetaminophen overdoses is selling paracetamol pre-combined in tablets either with an emetic or an antidote (Dargan et al., 2003). Paradote was a tablet sold in the UK which combined 500 mg paracetamol with 100 mg methionine, an amino acid formerly, used in the treatment of paracetamol overdose (Heptonstall, 2006; Daly et al., 2008).

There have been no studies so far on the effectiveness of paracetamol when given in combination with its most commonly used antidote, acetylcysteine (Chang, 2012). Calcitriol, the active metabolite of vitamin D₃, appears to be a catalyst for glutathione production (Garcion, et al., 2002). Calcitriol was found to increase glutathione levels in rat astrocyte primary cultures on average by 42%, increasing glutathione protein concentrations from 29 nmol/mg to 41 nmol/mg, 24 and 48 hours after administration, it continued to have an influence on glutathione levels 96 hours after administration (Garcion, et al., 2002). It has been proposed that co-administration of calcitriol, via injection, may improve treatment outcomes. Paracetamol ester prodrug with L-pyroglutamic acid etc.

Fig 4: **Acetylcysteine**: is the antidote for paracetamol toxicity
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