Acetaminophen Toxicity at Therapeutic Doses

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Abstract

Acetaminophen is the first line choice for pain management, but is also among the most important pharmacological causes of liver injury. It is considered safe at doses of 4g/day. However, acetaminophen at therapeutic dosage should be considered in the differential diagnosis of the acute liver injury. Alcoholic patients may have increased CYP2E1 activity and lower concentration of glutathione. This leads to higher levels of NAPQI, responsible for liver toxicity. Other mechanisms of toxicity may occur through induction of CYP 450 pathway like the use of Phenytoin and Simvastatin. Malnutrition and prolonged fasting shunt glucose precursors toward gluconeogenesis instead of glucuronidation. In cardiopulmonary disease, centrilobular zones are the most vulnerable to low oxygen delivery. They are the main site of glucuronidation and reservoir of liver CYP2E1. In the absence of sufficient oxygen necessary for glucuronidation, more acetaminophen is metabolized through the CYP450 pathway leading to higher NAPQI concentrations and therefore acetaminophen toxicity with centrilobular necrosis. The induced activity of CYP2E1 in obesity and NAFLD can favor acetaminophen hepatotoxicity in these situations. Diagnosis of liver injury with therapeutic doses of acetaminophen is challenging and requires a high index of suspicion. Acetaminophen level should be measured whenever the diagnosis is suspected. Acetaminophen related liver injury is dose dependent and may be prevented by reducing daily drug dose to 2 to 3 g/day in the presence of risk factors for liver toxicity.

Keywords: Acetaminophen, hepatotoxicity, drug-drug interaction, alcohol, viral hepatitis, therapeutic dosage

I. Introduction

Acetaminophen is a widely used analgesic and antipyretic in the world despite being the leading cause of acute liver failure,(1) and its current availability as an over-the-counter medication. Liver injury and fulminant liver failure related to acetaminophen is dose related and usually occurs with overdose. It may nevertheless occur at therapeutic doses especially under some predisposing conditions as in regular alcohol use or in the setting of an underlying liver disease. Literature about this entity is scarce and controversial. We proceeded to a literature review of the pathophysiology of acetaminophen induced hepatotoxicity at therapeutic dosage, predisposing conditions, diagnosis, and treatment.

II. Hepatotoxicity of acetaminophen

1. Acetaminophen metabolism

Acetaminophen is mainly metabolized via sulfation and glucuronidation pathways into nontoxic products (glucuronide and sulfate) that are excreted in the urine. Less than 5% of acetaminophen is converted via the CYP pathway, in particular CYP2E1, into a highly toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified through conjugation with glutathione (fig. 1). Following larger doses of acetaminophen, the accumulation of high levels of NAPQI leads to depletion of glutathione in the liver.(2)

2. Interaction with alcohol

In 1998, the FDA issued the alcohol warning for acetaminophen-containing products. Patients presenting an alcohol-acetaminophen syndrome are regular moderate to heavy drinkers who use therapeutic or modestly excessive doses of acetaminophen. Severe hepatotoxicity may complicate ingestion of as little as 4g or even lower therapeutic doses per day.(3) The signs of hepatotoxicity in these subjects included elevated liver enzymes with centrilobular necrosis.(4)

The effects of ethanol on CYP2E1 comprise a simultaneous increase in CYP2E1 concentration and an inhibition of its action. During acute heavy alcohol ingestion, alcohol competes with acetaminophen for interaction with CYP2E1. With chronic alcohol use, a combination of CYP2E1 induction and glutathione depletion results in an increased accumulation of NAPQI, leading to enhanced acetaminophen toxicity from doses usually within the therapeutic range.(5)

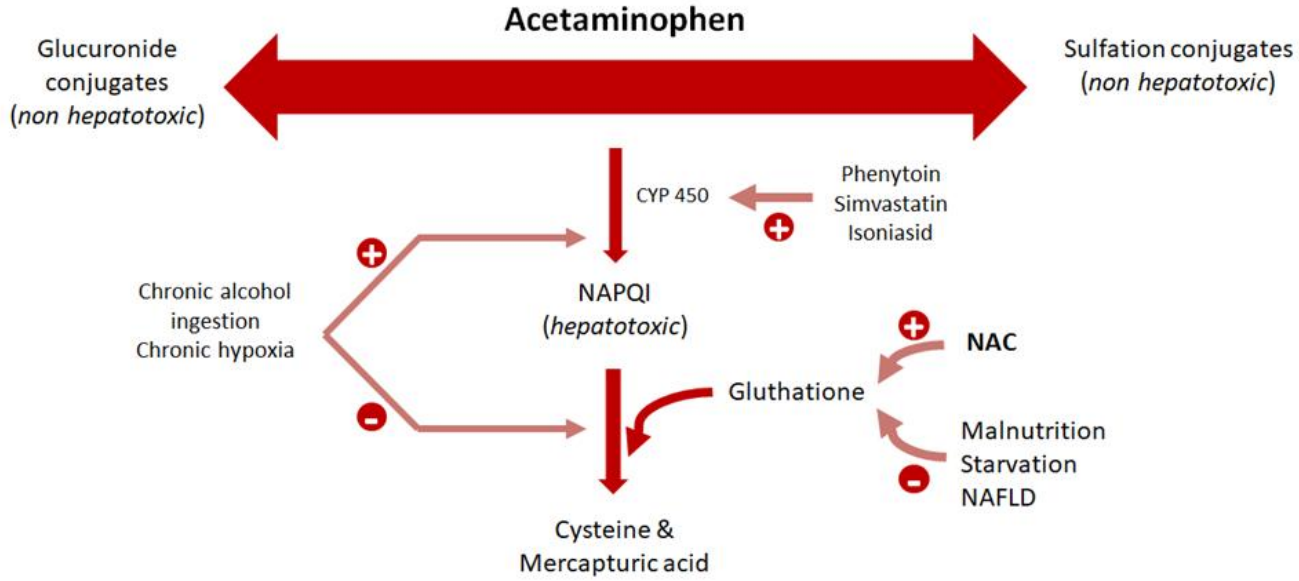

Figure 1: Influence of intervening factors affecting Acetaminophen metabolism pathway and toxic byproducts in the liver.

The effect of ethanol on CYP2E1 and NAPQ1 is dependent on the level of ethanol ingestion and the time elapsed between the last ethanol ingestion and acetaminophen intake. Animal studies have shown that if enough time is allowed for ethanol to be eliminated, NAPQI formation will be enhanced because of a highly induced CYP2E1 in the absence of competition between acetaminophen and alcohol, and the lack of the inhibitory action of alcohol on the enhanced cytochrome. The induction of CYP2E1 becomes significant after an abstinence of twelve hours, and the effects wanes by the fifth day after alcohol withdrawal.(6) Further to alcohol effects, poor diet, starvation and protein depletion in alcoholic patients reduce glutathione stores leading to a higher toxicity of a single dose of acetaminophen. In addition, alcoholic patients may be more predisposed to exceed the recommended doses of OTC drug and may present a higher tendency towards substance abuse.(7)

3. Drug-drug interactions

Hepatotoxicity is a well-known side effect of antituberculous agents. However, an interaction may exist between acetaminophen, isoniazid and rifampicin resulting in a more severe hepatotoxicity as compared to the use of either drug alone. Nolan et al have reported 2 cases of patients treated with antituberculous quadritherapy who experienced pronounced serum elevations in hepatocellular enzymes after receiving therapeutic doses of acetaminophen (2 to 4 g per day) for several days to relieve symptoms of malaise, fever, and sweats. Liver function tests returned to normal after few weeks when isoniazid and acetaminophen were discontinued.(8) Animal studies revealed that CYP2E1 induction occurs through stabilization of the enzyme without increasing its synthesis. Consequently, when isoniazid was taken in a regimen of 300 mg per day, inhibition of NAPQI production was observed. However, after discontinuation, NAPQI production was increased 24 hours after the last dose of isoniazid.(6)

CYP3A4 may also contribute to acetaminophen metabolism. Induction of this isoform may explain acetaminophen-induced hepatotoxicity in many patients. Induced CYP3A4 activity by simvastatin and phenytoin may enhance the conversion of acetaminophen to its hepatotoxic product NAPQI.(9;10)

Valproic acid increases mitochondrial cholesterol accumulation leading to subsequent glutathione depletion. (11) This increases the risk of acetaminophen related-liver injury.

4. Impact of chronic use of therapeutic acetaminophen

Acetaminophen is often used on a regular, daily basis for the treatment of chronic pain. Although patients with the afore-mentioned risk factors have a higher risk of developing toxicity with chronic acetaminophen administration, those without risk factors may also develop toxicity. Bolesta and Haber reported 4 cases of liver toxicity with reversible elevation of transaminases with acetaminophen therapy at doses $\leq$4 g/d, administered for $\geq$ 4 days, in patients with no other risk factors for toxicity.(12) Fulminant hepatitis after 10 days of treatment with recommended dosage of acetaminophen (720 mg/d) that improved after treatment with N-acetylcysteine has also been reported.(13)

In a randomized placebo-controlled trial, ninety-four patients without history of liver dysfunction randomly received for 12 weeks acetaminophen 2g/d or placebo. A single patient increased ALT to more than 3 times the upper limit of normal. Regular, daily use of acetaminophen at half the maximum recommended daily dose for 12 weeks in healthy population is associated

with a small elevation in mean ALT of probably no clinical significance. (14;15) Concomitant treatment with opioids does not seem to increase this effect. (15)

In another RCT comparing acetaminophen 4g/d or naproxen 750 mg/d for 6 or 12 months, in the setting of mild to moderate osteoarthritis pain, no hepatic failure or hepatic dysfunction were reported. No patients had values more than 2 times the upper limit of the reference range. These results suggest that long-term use of acetaminophen at recommended doses may not be associated with evidence of liver injury. However, because of data assessments intervals of 1 to 3 months, transient alterations in biochemical parameters would not be identified. (16)

5. Malnutrition and therapeutic dose of acetaminophen

Malnutrition is a well-documented risk factor for acetaminophen induced hepatotoxicity even at therapeutic dosage. In catabolic states, like fasting and malnutrition, glucose precursors, necessary for glucuronidation, are used for gluconeogenesis.(17) A 16-hour period is sufficient to deplete liver glutathione stores in mice.(18) Kurtovic and Riordan reported a case of 53-year-old woman who developed severe hepatotoxicity after she received daily 4g of acetaminophen under medical supervision following a period of fasting of approximately 20h. The same patient didn't develop hepatotoxicity when she received 1.3 g to 2.6 g per day of acetaminophen following an anal surgery and an equivalent fasting period. This case highlights the fact that acetaminophen hepatotoxicity, at least in the setting of severe malnutrition may be prevented by reducing the daily dosage of the medication.(19)

6. Acetaminophen and hepatitis C

Studies have shown that patients with HCV infection may be at increased risk of acute liver injury following supra-therapeutic acetaminophen.(20; 21) None of the studies have examined the safety of long term use of therapeutic doses of acetaminophen in the setting of chronic hepatitis C infection. Chronic inflammation may lead to sensitization to secondary xenobiotic-induced stress because many molecular events involved in the progression of liver injury are shared. A study that used HCV-Transgenic mice revealed that mitochondrial dysfunction in HCV infection may explain increased susceptibility in response to acetaminophen treatment.(22) Moreover, elevated CYP2E1 expression described during chronic hepatitis C, is induced by HCV NS5A and contributes to oxidative stress.(23) However, more research is necessary to assess the hepatotoxicity of therapeutic doses of acetaminophen in hepatitis C infection.

7. Acetaminophen toxicity in cardiopulmonary disease

The possibility that cardiopulmonary compromise could predispose to acetaminophen induced liver injury has received relatively little notice among clinicians. Bonkovsky et al. reported a case of 67-year-old man with chronic congestive heart failure who exhibited severe liver injury after short term ingestion of therapeutic doses of acetaminophen (1 to 3 g / day for 3 days) to relieve lower anterior rib pain. No other risk factors like alcohol abuse or malnutrition were implicated. Liver biopsy showed zone-3 necrosis with hepatocyte dropout, congestion and macrophage response. After recovery, the repeat liver biopsy revealed normal architecture in presence of minimal reactive changes of mild steatosis.(24)

Acinar zone III constitute the detoxifying zone for acetaminophen. It is characterized by a high concentration of CYP2E1. This same region is most sensitive to perfusion disorders and hypoxemia because of a decreasing oxygen gradient between zone I and zone III as in right-sided heart failure. Limitation of oxygen delivery could result from a compromised cardiac function, pulmonary function or both. Hypoxemia and hypo-perfusion make cells in acinar zone III more vulnerable to oxidative and chemical-induced injury. Glucuronidation characterizes the predominant pathway for detoxication of acetaminophen and depends critically on oxygen supply to hepatocytes. Glucuronidation pathway and the highest concentrations of cytochromes P-450 are mainly localized in the centrilobular regions of the liver which normally receive lower O2 concentrations than cells in the periportal regions. Reduced glucuronidation leads to an enhancement in metabolism by cytochrome P450-catalyzed reactions. The increase in P450-catalyzed reactions consequent to a decrease in glucuronidation could result in greater susceptibility of centrilobular cells to acetaminophen toxicity. In the setting of hypoxemic conditions alone, GSH level may be normal. However, when a higher level of GSH is needed as in chronic acetaminophen consumption, GSH synthesis may not increase sufficiently. Increased sensitivity to oxidative stress may also be explained by the decreased production of glucose-6-phosphate and NADPH that are required for regeneration of GSH from GSSH.(25) During chronic hypoxia, the additive effects of decreased O2 supply, reduction of glucuronidation, enhanced CYP450 activity with decreased hepatic GSH regeneration may explain the risk of centrilobular necrosis, even with therapeutic doses of acetaminophen.(26)

8. Acetaminophen in acute viral hepatitis

Fever during the prodromal phase of viral hepatitis may lead almost always to the use of acetaminophen. Polson et al have revealed that patient who had a viral hepatitis with detectable acetaminophen level on admission, had higher transaminases level and more severe coagulopathy. This observation suggests that acetaminophen may enhance hepatocellular injury in the setting of viral hepatitis. In the setting of acute hepatitis A, acetaminophen was associated with higher risk of encephalopathy and higher bilirubin level.(27;28) The use of acetaminophen at therapeutic doses in viral hepatitis is associated with higher bilirubin level and a lower factor V.(28).

9. Acetaminophen in Cirrhotic patients

Pain management is a big challenge in cirrhotic patients. Acetaminophen is believed to be the safest drug because of a lower risk of encephalopathy and renal failure as compared to opioids and NSAIDs respectively. Because of the lack of data concerning acetaminophen dose-response in chronic liver disease, dosing recommenddations are extrapolated from pharmacologic data, small studies and actual observed clinical outcomes.

The decreased plasma clearance of acetaminophen in patients with cirrhosis is multifactorial: ineffective hepatic perfusion, intrahepatic or extrahepatic shunting and especially a reduced rate of hepatic metabolism. Patients with portal hypertension develop portosystemic shunts and a variable proportion of the portal blood flow bypasses the liver depending on the importance of these shunts. Zapater et al have shown that cirrhotic patients with esophageal varices and portal hypertension have a lower clearance of acetaminophen and earlier effective plasmatic concentrations of acetaminophen (15 min vs. 1 hour in healthy patients) with faster analgesic effect.(29)

The plasma half-life of acetaminophen is prolonged from an average of 2.1 hours in control patients to 3.7 hours in patients with hepatic cirrhosis. The more severe the degree of liver function impairment, the more reduced the plasma clearance of acetaminophen. The plasma levels are 2 to 3 times higher in the patients with cirrhosis indicating that a corresponding doe reduction may be recommended in this setting.(30) Although the half-life may be prolonged in cirrhotic patients, the CYP450 activity is not enhanced in this situation and glutathione may be sufficient to avoid acetaminophen hepatotoxicity.

Reactive hepatotoxic intermediates, and consequently the risk of liver damage, are not increased with therapeutic doses of acetaminophen in patients with chronic liver disease.(29) Khalid et al compared decompensated cirrhotic patients, with compensated cirrhotic patients and non-cirrhotic patients who received over the counter analgesics. The study showed that acetaminophen at a maximal dose of 3g/day for 2 days or 1g / day for 25 days is not associated with acute hepatic decompensation.(31) In the absence of contributory factors, such as malnutrition, underweight, and heavy alcoholism, there is no strong evidence of glutathione store depletion in chronic liver disease nor an increased risk of hepatotoxicity in the setting of chronic liver disease.(32) None of the various scores used for the assessment of liver function including Child Pugh score and meld score, is sufficient to determine a safe drug dosing in these patients.(33)

Although current recommendations suggest a maximal dose of 2 to 3 g/day of acetaminophen, up to 4 grams per day is well tolerated by most cirrhotic patients in the short term. The maximal dose should be inversely correlated with the severity of portal hypertension, associated shunting as well as comorbidities in cirrhosis mainly malnutrition and alcoholism.

10. Acetaminophen in NAFLD and obese patients

In the setting of obesity and NAFLD, the mechanisms of acetaminophen induced liver toxicity might be more complex than expected although different hypothesis have been put forward. There is some evidence that CYP2E1 induction could favor APAP-induced hepatotoxicity in these situations. It's also expected that the presence of necrosis and inflammation with mitochondrial dysfunction in NASH could be associated with a higher risk, as compared to simple fatty liver. Moreover, reduced glutathione stores in NAFLD may reduce NAPQ1 detoxification, predisposing to higher risk of liver injury (34). Michaut et al have used hepaRG cell lines to reveal that high level of insulin in NAFLD was responsible for an increased CYP2E1 mRNA and protein expression in a concentration-dependent way leading to higher levels of NAPQI.(35) This increase of CYP2E1 expression is hypothesized to play a role in NAFLD pathogenesis.(36)

In presence of these protective factors (increased glucuronidation and volume dis-tribution), not all obese people will present acetaminophen hepatotoxicity. The occurr-ence and outcome of acetaminophen induced liver injury in an obese individual with NAFLD might depend on the delicate balance between metabolic factors that favor hepatic cytolysis and others that are directly, or indirectly, hepatoprotective.(34)

Van Rongen et al compared morbidly obese patients to non-obese patients and found that obesity leads to increased glucuronidation capacity accelerating acetaminophen clearance with increased volume of distribution. As such, obese patients may need higher loading and maintenance doses

of acetaminophen. That study showed that morbidly obese patients also have increased CYP2E1 expression precluding this dose adjustment.(37)

There is no current information as to whether NAFLD might be aggravated in some patients by therapeutic doses of APAP. A 1-month treatment with therapeutic doses of APAP significantly enhanced plasma aspartate aminotransferase (AST) activity by 45% in mice fed a high-fat diet, whereas this increase was only 19% in mice fed a normal diet.(38) Clearly, further investigations are warranted to determine whether APAP can be safely prescribed for chronic treatment, in particular patients suffering from obesity and NAFLD.

III. Diagnosis of acetaminophen hepatotoxicity

Most reports concerning acetaminophen related hepatitis are related to high dose ingestion either accidentally or in a suicidal attempt. Early symptoms may include nausea, vomiting and fatigue. Mild hepatic tenderness may exist.(39) Transaminase level, initially normal, increases after a latent period of 24 to 48 hours, or as early as 12 hours after a massive ingestion, then peaks after 48 to 72 hours.(40) The AST level can reach 10 000 UI/L or more and may be more elevated than ALT level. Maximal liver injury may typically occur between 3 to 5 days with jaundice, coagulopathy, and encephalopathy. Acetaminophen poisoning may also lead to metabolic acidosis and acute kidney injury. The presence of acute liver failure, prothrombin time more than 100s, grade 3 or 4 encephalopathy, cerebral edema, renal failure, and metabolic acidosis (pH < 7.3) are indicators of poor outcome.(41) The diagnosis is easily confirmed by measuring acetaminophen blood level. Patients who present after a single acute ingestion of acetaminophen should have the blood level of acetaminophen measured 4 hours after ingestion or as soon thereafter as possible. Blood level within 4 hours of ingestion may underestimate the extent of exposure because of delayed gastric emptying. Those who have a timed serum acetaminophen concentration (i.e., as measured between 4 hours and 24 hours after ingestion) that falls above the study line on the Rumack-Matthew nomogram are considered to be at risk for toxic effects even if no clinical or laboratory evidence of hepatic injury is present. Such patients should be treated with N-acetylcysteine.(42)

Acetaminophen heaptotoxicity is difficult to diagnose in the setting of the chronic therapeutic doses. The most important clue for suspecting acetaminophen toxicity is a thorough enquiry of patient's medication intake. Patients should be asked about all the ingested drugs, the total ingested dose, the specific product, the pattern of ingestion (single or repeated dosing) and the duration of its use. Acetaminophen hepatotoxicity should be suspected in alcoholic patients, malnourished or in patients with chronic liver disease even with therapeutic doses. For example, chronic alcoholic patients with acetaminophen hepatotoxicity usually seek help later with symptoms of hepatotoxicity and high aminotransferase levels (ALT > 1000) while the acetaminophen blood level may be low or undetectable. A dramatically high level of ASAT of more than 1000 UI/L and long prothrombin time (>30 s) are not typical features of alcoholic hepatitis. Other etiologies, like acetaminophen toxicity, should be suspected.(43) It should be noted that the nomogram is approved for single overdose with precise time of ingestion. It cannot be used as an assessment tool of the risk after repeated overdoses, chronic acetaminophen use, when the time of ingestion is unknown, or when patients present beyond 24 hours.(44) Therefore, it is

less useful to predict hepatotoxicity and guide treatment in the setting of a repetitive therapeutic dose of acetaminophen. However, acetaminophen blood level should always be measured when the diagnosis is suspected. Acetaminophen detected more than 24 hours after the last intake may be suggestive of acetaminophen toxicity or as a contributing factor to another underlying cause of liver disease. On liver biopsy, Zone 3 or centrilobular hepatocellular necrosis is characteristic of APAP injury. The centrilobular region is the area of greatest concentration of CYP2E1, and therefore the site of maximal production of NAPQI.(41)

1. Future diagnostic perspective

Although diagnosis of acetaminophen toxicity seems easy with high dose ingestion, there still remain multiple difficulties in diagnosis when the presentation is delayed or in chronic therapeutic use of acetaminophen. NAPQI binds to Hepatocellular proteins when glutathione stores are depleted. The resulting acetaminophen-cysteine (APAP-CYS) protein adducts (APAP bound to cellular proteins via cysteine residues) can be quantified by high-pressure liquid chromatography with electro-chemical detection (HPLC-EC). These adducts localize in the centrilobular hepatocytes. These cells undergo lysis and release both adducts and hepatic aminotransferases in the serum.(45) Serum adducts are considered a specific biomarker of acetaminophen exposure. Their concentration has been found to correlate with acetaminophen-induced hepatotoxicity. This test may be helpful to detect acetaminophen hepatotoxicity when the history is unclear or when the patient presents more than 24h after the last overdose. Serum adduct concentration above 1.1 µmol/L are described as highly specific for acetaminophen-induced hepatotoxicity whereas the expected range for therapeutic dosing is less than 1.1 µmol/L. (45;46;48) Unfortunately, the measurement of this adducts is not available in most centers.

In the setting of overdose and supra-therapeutic doses of acetaminophen, the product (serum APAP concentration (µmol/L) × alanine transaminase (IU/L)) has been validated to predict hepatotoxicity from acetaminophen overdose. A product more than 10 000 mg/L × IU/L was associated with a very high likelihood, and less than 1 500 mg/L × IU/L with a very low likelyhood, of developing hepatotoxicity in patients treated with N-acetyl-cysteine. (49;50) The use of this equation is probably not useful in the setting of therapeutic use of acetaminophen.

Circulating extracellular microRNA biomarkers can serve as a powerful tool for early diagnosis of acetaminophen induced liver injury. Hundreds of microRNAs become dramatically elevated in the plasma or serum of acetaminophen overdose patients and then return to normal during successful treatment with N-acetylcysteine. Variation of micro-RNAs level may precede the variation of transaminases levels and may help predicting hepatotoxicity following acetaminophen overdose. MicroRNAs could also serve as a more sensitive and specific signatures to distinguish APAP hepatotoxicity from other causes of liver disease.(51) In patients with acetaminophen-induced liver injury, circulating microRNA-122-5p has been reported to be increased around 100-fold compared to controls. High levels of microRNA-122-5p combined with low levels of microRNA-483-p were more sensitive than ALT for reporting liver injury at hospital presentation.(52) These biomarkers may offer a real promise that allow the clinician to move from using acetaminophen concentration or dose ingested alone as the decision tool, especially when the Rumack-Matthew nomogram cannot be used to predict risk for hepatotoxicity.

IV. Prevention of acetaminophen induced liver toxicity

Until now, many clinicians do not believe that acute liver injury can be a potential complication after regular ingestion of acetaminophen at therapeutic doses. As aforementioned, subjects who regularly consume alcohol but are recently abstinent at the time of acetaminophen administration have higher levels of CYP2E1 and increased production of NAPQ1.(53) Patients with alcoholic cirrhosis who are actively drinking would be more susceptible to develop acute-on-chronic liver injury from lower doses of acetaminophen.(31) Acetaminophen doses should be reduced to 2 g/day, or preferably avoided in chronic alcohol users.(54) Depleted glutathione stores during malnutrition and fasting states are high-risk conditions for acetaminophen toxicity at therapeutic doses in chronic liver disease. Owing to the changes in the pharmacokinetics and the vulnerability of this population, it seems reasonable to limit the adult daily dose to 2 g/day. Physicians should remain alert to any symptoms indicating a possible aggravation of the hepatic function. Acetaminophen at a maximal daily dose of 3 g/day (for up to 2 days) or at a daily dose of 1 g/day (for up to 25 days) does not appear to be associated with acute hepatic decompensation.(31) Acetaminophen at a dose less than 2 gm/day is a reasonably safe option. Patients with cirrhosis having visceral or musculoskeletal pain should be treated with acetaminophen less than 2-3 g/day.(55) To reduce the risk of hepatotoxicity, the FDA requires that pharmaceutical companies limit the amount of acetaminophen to 325 mg per tablet and that all the formulations containing the drug have a black box warning for potential liver damage.(56) These products were withdrawn by the manufacturers at FDA's request to protect consumers from the risk of severe liver damage. The British National Formulary version 60 advises that IV acetaminophen should be limited to 3 g/day in patients with hepatocellular insufficiency, chronic alcoholism, and chronic malnutrition.(57)

V. Conclusion

Acetaminophen is the most widely used analgesic but also the leading cause of acute liver failure. Liver toxicity may occur even at therapeutic doses especially in alcoholic patients, in subjects with chronic liver disease, NAFLD, cardiopulmonary disease, malnutrition, or when acetaminophen is concurrently used with other drugs that stimulate the CYP pathway. Liver toxicity of acetaminophen is dose dependent and can be prevented through lowering the daily dose of acetaminophen to 2-3g/day when risk factors for hepatotoxicity are suspected. In malnutrition, chronic alcohol, and acute hepatitis, acetaminophen intake should be avoided. In most cases liver toxicity implies mild abnormalities in liver function tests; it is nevertheless a diagnostic challenge in the setting of other concomitant liver diseases or in the setting of polymedicated patients. A high index of suspicion is crucial for early diagnosis, acetaminophen discontinuation, and prompt initiation of treatment.

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