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Review Article

PARACETAMOL POISONING: A REVIEW

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ABSTRACT

Paracetamol (Acetaminophen) is widely available analgesic and antipyretic, is the leading worldwide causes of drug overdose and acute liver failure. Single overdose ingestion and therapeutic misadventure may cause hepatotoxicity. Several factors such as concomitant alcohol use or abuse, concurrent medications, genetics factors, nutritionals factors, chronic liver disease, pregnancy and age can influence the susceptibility and severity of paracetamol hepatotoxicity. Early manifestation of paracetamol hepatotoxicity is nonspecific but requires prompt recognition by physicians. N-acetylcysteine is an effective antidote for paracetamol overdoses. Early treatment with NAC prevents the formation of toxic metabolites that leads to hepatic injury. The king college hospital criteria is the most often used to determine which patients are die from fulminant hepatic failure and other criteria included phosphate, lactate and MELD score. This review article discusses the mechanism, factor influence, clinical features, and treatment of paracetamol overdose based on recent research in this area.

Keywords: Paracetamol poisoning, Drug overdose, N-acetylcysteine, hepatotoxicity, Fulminant hepatic failure, Liver transplant.

INTRODUCTION

Paracetamol (Acetaminophen) is a safe, effective analgesic and antipyretic, has been extensively used around the world since 1955[1]. It is available as various formulations, a single-ingredient medication (immediate release and extended release tablets/capsules, suspensions, rectal suppositories and for intravenous use) and as a component of numerous combination and prescription product used for pain and as an antipyretic. Despite its safety when used properly, Paracetamol is the most common overdoses reported to poison centre. Serious toxicity results in hepatic injury, which may progress to fulminant hepatic failure and death [2]. Paracetamol overdose account for 50% of self-poisoning hospital admission and the most common causes of acute liver failure in United States [3]. Potential liver damage, predicted from blood paracetamol concentration and time from ingestion, can be prevented by prompt treatment with antidote. Single overdose ingestion usually follows attempted self-poisoning and exceeding 15 to 25 g may causes severe liver injury that is fatal in up to quarter of the cases [4, 5]. However 30-50% of cases of paracetamol hepatotoxicity admitted to hospital nowadays result from therapeutic misadventure, where the daily dose may not have greatly exceeded the recommended safe limits but where specific risk factors are present[5].

Epidemiology:

Approximately 0.01% of the US population and 0.02% of the Australian population are assessed in hospital each year because of paracetamol poisoning. In 2009, the American association of poison control centre, national poison data system reported 401 deaths caused by paracetamol or paracetamol combination product [6]. In United States, paracetamol overdose is the leading reason for calls to the poison control centers (> 100000 per years) and accounts annually for more than 56000 emergency room visits, 2600 hospitalizations and approximate 450 deaths caused by acute liver failure [4].

Pharmacology and toxicity:

The therapeutic dose is 325 to 1000 mg/dose (10-15mg/kg/dose in children), given every 4 to 6 hours with maximum recommended daily dose of 4 g. Paracetamol is rapidly absorbed from gastrointestinal tracts with peak concentration achieved within 90 minutes of a therapeutic dose, with over dose ingestion peak concentration being achieved within 4 hours or may be delayed beyond 4 hours, when use of extended release preparations. The presence of food in the stomach may delay the peak but not the extent of absorption. Distribution is rapidly with a volume of distribution of about 0.9L/kg and minimal protein binding at therapeutic concentration [7]. Therapeutics serum concentrations of paracetamol range from 10-20µg/ml. The serum half-life is 2-2.5 hours; however, it is prolonged to more than 4 hours in patients with hepatic injury and chronic liver disease and those who use ingested extended release preparations [7].

At therapeutic dose, approximately 85% to 90% of paracetamol undergoes phase II conjugation to sulfate and glucoronidated metabolites, which are then excreted in the urines [7, 8]. About 2% of paracetamol is excreted in the urine unchanged. The remaining paracetamol upto 10% undergoes phase 1 oxidation by the hepatic cytochrome P-450 pathways to a toxic, highly reactive intermediate, N-acetyl-Para-benzoquinoneimine(NAPQI)[7, 8]. Small amount of NAPQI produced from normal doses of paracetamol is

rapidly conjugated by hepatic glutathione, forming nontoxic mercaptate and cysteine compounds that are excreted in the urines [7-9].

At toxic doses of paracetamol, sulfation and glucoronidation pathways become saturated and more paracetamol is metabolized through the hepatic cytochrome P-450 pathways to NAPQI [8]. An increase in production of NAPQI, results in depletion of hepatic glutathione and when glutathione stores are depleted by about 70% to 80%, NAPQI bind to hepatocytes causing cellular injury [8, 10]. In the absence of hepatic glutathione, NAPQI bind to cysteine groups on hepatocytes molecules forming NAPQI- protein adducts. This process is an irreversible step that leads to oxidative injury and hepatocellular necrosis [8]. The mitochondrial damage, nuclear DNA fragmentation and lipid peroxidation plays an important role in paracetamol induced hepatocellular damage [8, 11, 12]. Hepatic glutathione depletion contributes to oxidative stress, activation of stress protein and gene transcription mediators and alteration in the liver innate immune system. The early cell necrosis causes the release of various chemical mediators, which enhance proinflammatory cytokines and chemokine formation from macrophages [13]. Although proinflammatory mediators recruit inflammatory cells into the liver, causes significant direct cytotoxicity.

Factors influences paracetamol related hepatotoxicity:

The ingested dose of paracetamol seems to be the most important factors determining the development and severity of paracetamol hepatotoxicity. In addition, the pattern of uses and various factors can influence the susceptibility to paracetamol hepatotoxicity through several mechanisms including decreased capacity for glucoronidation or sulfation, excessive CYP activity and depletion of hepatic glutathione stores, which is described below.

Dose and pattern of uses:

A single acute ingestion of greater than or equal to 7.5 to 10 g in adults or 150 to 200 mg/kg in children older than 6 years is likely to causes hepatotoxicity and require prompt evaluation and therapeutic intervention. Repeated overdoses of greater than or equal to 10 g in 24 hours period or greater than or equal to 6 g per 24 hours period for greater than or equal to 48 hours may leads to hepatotoxicity and patient should undergo evaluation in health care facility. The safety of short term and long term use of paracetamol at maximum recommended dose is 4 g is recommended [1, 14].

Patients	Maximum single dose	Minimum dose intervals	Maximum dose in 24 hours
Adults	1 g	4 hours	4 g
Children 6-12 years	500 mg	4 hours	2 g
Children 1-5 years	240 mg	4 hours	960 mg
Infants 3-12 months	120 mg	4 hours	480 mg

Table 1: Recommended maximum dose of paracetamol[[1].

Alcohol:

Acute ingestion of alcohol is not risk factors for paracetamol hepatotoxicity and may actually be protective by competing with paracetamol for CYP2E1 [15, 16]. Chronic alcohol ingestion may potentiate paracetamol hepatotoxicity by upregulating CYP2E1 and decrease hepatic glutathione synthesis [5, 8, 17]. Chronic alcohol ingestion enhances CYP2E1 activity about two fold by enzyme stabilization and increase synthesis [5, 8]. In addition, Alcoholics are often malnourished and associated with depleted hepatic glutathione stores, which further predisposing hepatotoxicity.

Medications and Herbs:

The anticonvulsants agent like phenobarbitone, Phenytoin, Carbamazepine and antituberculosis agents like isoniazid, rifamicin may predispose to paracetamol hepatotoxicity by increase production of NAPQI by ways of oxidative pathways [8, 18, 19]. Some herbs and dietary supplements are inducers of CYP (e.g. - garlic, grape fruit juice, and germander and potentiates paracetamol hepatotoxicity [20]. Zidovudines and trimethoprim-sulfamethoxazole may augment paracetamol hepatotoxicity by competitive use of the glucoronidation pathway and with subsequent increased metabolism towards CYP[21].

Genetic factors:

Genetic polymorphism in the CYP is enzymes can be associated with an excessive or diminished oxidative metabolism of paracetamol but clinical relevance to toxicity is unknown [8, 22, 23]. Impaired glucoronidation in patients with Gilbert syndrome seems to augment paracetamol toxicity [24].

Age:

The metabolism of paracetamol is age dependent, by which older patients are more susceptible to develop hepatotoxicity compared with young children after than acute over doses [25, 26].

Nutritional status:

In chronic alcoholic consumption person, malnutrition and fasting state may potentiate paracetamol hepatotoxicity by reduced capacity for hepatic glucoronidation and become depletion of hepatic glutathione stores [8, 27, 28]. Without chronic alcohol consumption the effect of malnutrition and fasting on paracetamol hepatotoxicity is unclear. The hepatic glutathione stores are reduced by about 30 % in patients with protein calorie malnutrition such as anorexia nervosa [29].

Chronic liver disease:

Patients with cirrhosis CYP activity is low and hepatic glutathione stores may be depleted but not to critical levels [8, 30]. Patients with chronic liver disease, who do not regularly consume alcohol, are not significantly increased risk for developing paracetamol hepatotoxicity [8, 30]. The paracetamol of dose less than 4 g/day is seems to be safe for short term dose in patient with cirrhosis.

Pregnancy:

Paracetamol is the most common drug overdose in pregnancy. The metabolism of paracetamol is altered (increased clearance caused by increase activity of glucoronidation and oxidative pathways) during

pregnancy, there is an insufficient evidences to suggest that pregnancy is predisposing factor for paracetamol hepatotoxicity. Paracetamol cross the placenta at toxic dose may harm maternal and fetal hepatocytes [31, 32].

Clinical manifestation:

The early manifestation of paracetamol overdose are frequents, mild and nonspecific and include nausea, vomiting, malaise and abdominal pain. The increase in episodes of vomiting at first presentation seems to be a risk marker of subsequent hepatotoxicity [33]. These symptoms may improve over the first 24 hours, progressive hepatic injury manifest as early as day 2 to 3 with right upper quadrant pain and tenderness. The marked elevation of serum aminotransferase (often > 3000 IU/L), which typically start increasing within 24 to 36 hours and peak around 72 hours after overdose but may increase as early as 12 hours after a massive ingestion [34]. The aspirate aminotransferase (AST) can be greater than 10,000 IU/L and often more elevated than aminotransferase. Maximal liver injury typically peaks between 3 to 5 days after ingestion and may have feature of jaundice, coagulopathy and encephalopathy [35]. Recovery or progression to fulminant hepatic failure occurs over the following several days. The prothrombin times that continue to increase beyond 4 seconds after overdose and with a peak prothrombin time greater than or equal to 180 seconds are associated with approximately 90% mortality without liver transplantation.

Renal injury, oliguria and acute renal failure are also seen but less commonly. Maximal renal injury lags beyond peak liver injury and recovery is also more protracted [36]. Isolated nephrotoxicity without hepatic injury rarely occurs [37, 38]. Renal failure may also see with fulminant hepatic failure and hepatorenal syndrome. The mental status is typically clear after a paracetamol overdose unless altered by co ingested centrally acting drugs. However massive paracetamol overdose may cause coma [39, 40]. Metabolic acidosis is another uncommon finding early in course of paracetamol poisoning.

General approach and diagnostic tools:

General approach begins with careful history taking and physical examination. The exact time and amount of paracetamol intake and 4 hours paracetamol level should be obtained. The prognosis is worse if they are abnormal at presentation [41, 42]. Other tests, such as hepatic biochemical tests, blood urea, serum creatinine, sodium, potassium should be done in patients with repeated overdose and those who present more than 8 hours after ingestion. Investigation for possible coingested substance and other causes of hepatitis may require, especially in those with uncertain history. Ketones on urinalysis and low blood urea concentration can indicate starvation or poor nutrition, which increase the risk of liver damages.

Evaluation after acute single overdose:

The Rumack –Mattew nomogram is valuable tool for handling patients with single acute ingestion who present to a health care facility within 24 hours [35, 43-45]. The nomogram was constructed in the 1970 to estimate the likehood of hepatotoxicity caused by paracetamol for patients with a single ingestion at known time [35, 43-45]. To use the nomogram, patient serum paracetamol concentration is plotted in line with time interval from ingestion.

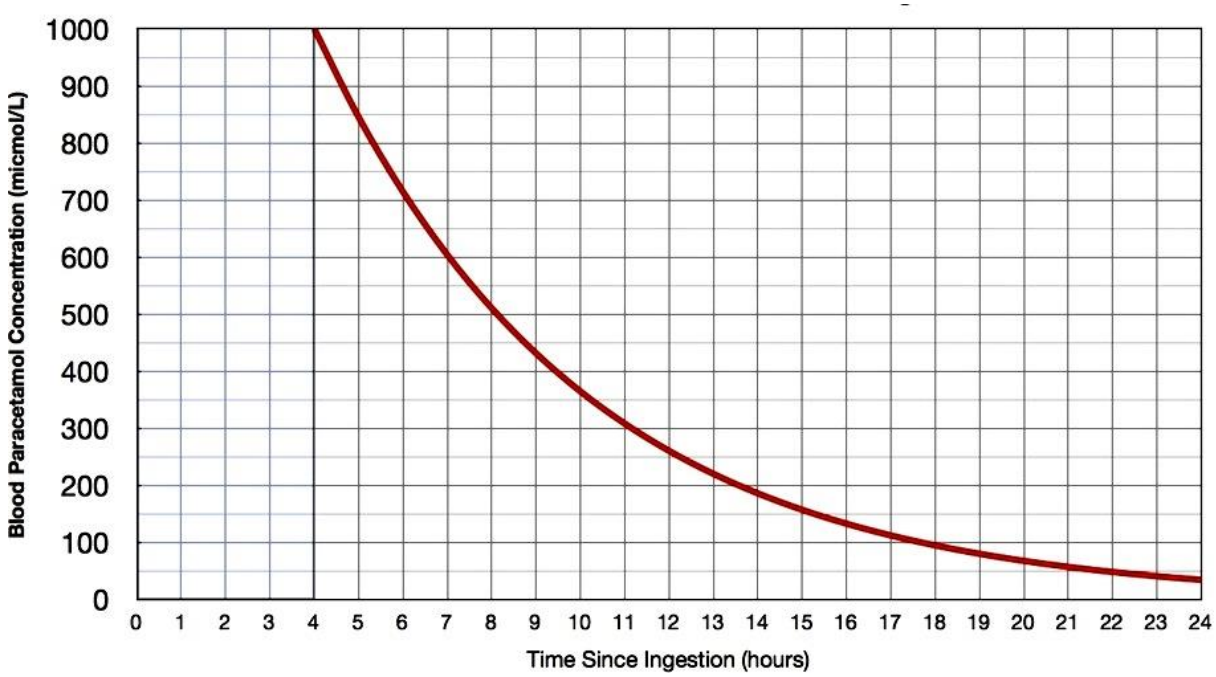

Figure 1: Rumack-Mattew nomogram. Paracetamol concentration shown on the Y axis and time from overdose on the X axis

Patients with paracetamol level above a line between 200 µg/ml at 4 hours and 25 µg/ml at 16 hours after ingestion, known as 200 line or probable toxicity line are the risk of developing several hepatotoxicity (defined as AST > 10000 IU/L) in which N-acetylcysteine (NAC) treatment is recommended even in the absence of clinical or laboratory evidence of toxicity at the time [35, 36, 43-45]. Without NAC treatment, patient with paracetamol concentration above 200 lines, have an approximate 60 % incidence of hepatotoxicity with 5% mortality.

Patients with paracetamol concentration above the parallel 300 lines or high toxicity line have a subsequent 90% incidence of several hepatotoxicity with 24% mortality [35, 36, 43-45].

After the generation of these data, the FDA then imposed an arbitrary 25% safety margin on the 200 line, which resulted in a parallel line starting at 150µg/mL at 4 hours, known as the 150 line or the treatment line and that have been commonly used in United States[46, 47].

It should be noted that the Rumack-Matthew nomogram was developed for single overdose with precise time of ingestion. Therefore it cannot accurately assess risk after repeated overdose, acute overdose of a sustained release product or when time of ingestion is unknown or patients present beyond 24 hours [48].

Evaluations after Repeated overdose:

Patients are often present after several days of ingestion with symptom in which hepatotoxicity may have already begun. They are likely to develop hepatotoxicity, if they have significant symptom and sign. Serum paracetamol concentration should be measured. Based on limited evidences, patient with supratherapeutic paracetamol level of more than 20 µg/mL are risk of developing subsequent hepatotoxicity and therapy with

NAC is suggested even if ALT level are normal[44]. Treatment with NAC seems unnecessary if serum APAP is undetectable or less than 10 µg/mL in asymptomatic patients with normal ALT levels. Patients with history of excessive paracetamol intake and who have elevated ALT level should receive NAC treatment even with undetectable serum APAP [33, 44].

Evaluations after established hepatotoxicity and liver failure:

Cautions monitoring of clinical and laboratory parameters is vital because greater than 90% of cases with paracetamol hepatotoxicity can be expected to resolve spontaneously [49]. The patients with clinical sign indicating acute liver failure (encephalopathy, coagulopathy, and acidosis), should be transferred to intensive care unit and a facility to liver transplantation is available [50, 51]. Apart from specific antidote, general evaluation and management of acute liver failure from paracetamol are not much different from ALF from other causes [51-53]. Although paracetamol induced ALF is associated with more favorable outcome compared with all other causes of ALF, it has a high mortality (30%) without LT [49]. One of the most widely used prognostic models was developed at king college in London, United Kingdom table-2, [53-55]. Based on differences on prognosis, king college criteria categorized patients into two groups: non paracetamol and paracetamol induced ALF. Without LT patients with paracetamol induced ALF who met the following criteria had very high mortality (80-90%)[8, 54, 55] and these patients deserve consideration of Liver transplantation. Although it is the best prognostic model available to date where in LT free survival has been evaluated. Overall king college criteria have proved to have acceptable specificity but relative low sensitivity to determine outcome. It is still the most validated and clinically useful prognostic model for paracetamol induced ALF, which is adopted by most transplant centre and by American association for the study of the Liver [8, 54-58]. The model of End stage liver disease is also useful in paracetamol induced ALF but has not proven to be a better discriminator than king college criteria or international normalized ratio (INR) alone [59].

Following are the criteria for paracetamol induced acute liver failure.

Indications

- Arterial PH < 7.3 or blood lactate > 3 mg/dl: after adequate volume resuscitation, irrespective of the grade of encephalopathy.
- **OR**
- Blood lactate > 3.5 mg/dl: after early volume resuscitation.

OR three of the following.

- Grade III or IV encephalopathy
- Prothrombin time> 100 seconds or INR > 6.5
- Serum creatinine > 3.4 mg/dl

Table 2: King's College criteria for paracetamol induced acute Liver failure [8, 53-55].

Management of paracetamol overdose:

Following are the way of management of paracetamol overdose:

Gastrointestinal decontamination:

Activated charcoal is effective at limiting the absorption of paracetamol when given within 4 hours after overdose and recommended in all patients who present early after paracetamol ingestion, unless there is contraindication (unsecured airways or gastrointestinal tract injury) [60-63]. Patients who present after 4 hours after ingestion are unlikely to benefit from activated charcoals, except in whose ingested extended release paracetamol preparation or coingested drugs that delays the gastric empty time. Gastric lavage and induced emesis are not usually recommended because they seem to be less effective and no additional benefits when activated charcoal is given [62, 63].

N-Acetylcysteine:

N-Acetylcysteine (NAC) is an effective antidote for paracetamol poisoning. When administered early after an acute paracetamol overdose, NAC provide cysteine for the replenishment and maintenance of hepatic glutathione stores, enhances sulfation pathways of elimination and may directly reduces NAPQI back to paracetamol[64, 65]. NAC reduces the incidences of hepatotoxicity and progression to FHF, when administered within the first 8 hours following an acute overdose. In a patient who receives NAC within first 8 hours after an acute overdose, the risk of hepatotoxicity is less than 5 % whereas delays beyond 10 hours are associated with increased risk of hepatic injury [45, 47, 66-68]. NAC should be initiated within 8 hours of ingestion, if the patient's paracetamol level plots above the treatment line (the 150 line) on the Rumack Mattew nomogram, shown in figure-1. If the paracetamol level will not be available by 8 hours post ingestion, NAC should empirically be stated.

Patients with hepatic injury also benefits from NAC that showed improved transplant free survival in patients with paracetamol induced FHF [69, 70]. NAC improves hepatic perfusion, oxygen delivery and extraction in patients with paracetamol induced FHF [70]. Other beneficial effects included scavenging of reactive oxygen, nitrogen species and improved mitochondrial energy productions [71, 72].

NAC is available both orally and intravenously. A 20-hours IV infusion of NAC has been widely used worldwide since this schedule was demonstrated effective[67]. This regimen includes a loading dose of 150 mg/kg IV over 15 minutes followed by 50 mg/kg over the next 4 hours (rate 12.5 mg/kg/h) and then 100 mg/kg over the next 16 hours (rates 6.25mg/kg/h). For patients weighing more than 100 kg, the US manufacture of IV NAC is recommended dosing equivalent to a 100 kg person. The infusion is now more commonly given over 21 hours with the loading dose given over 60 minute rather than 15 minutes to reduce the incidences of anaphylactoid reactions.

The standard oral doses of NAC is a 140 mg/kg loading dose followed by 70 mg/kg orally every 4 hours for total of 18 doses over 72 hours[47]. Although the two regimens are very different in duration and total doses but they are very effective for treatment of acute paracetamol overdose [73]. Shorter course of oral NAC have been studied and seem to be safe and effective. NAC will be discontinue after a minimum of 20 hours

of treatment, if a repeat paracetamol level was less than 10 μg/mL and there was no increase in serum aminotransferase or INR level is <1.3.

An alternative IV regimen has also been investigated in patients with acute paracetamol overdose presenting within 24 hours of the overdose. This regimen consisted of 140 mg/kg NAC as a loading dose then 70 mg/kg every 4 hours for 48 hours. This regimen was equally effective to the standard 72 hour oral and 20.25 hours IV courses [74]. Following an acute overdose, treatment should not be delayed beyond 8 hours after acute ingestion because of dramatic protective effect when given within this frame box [68]. The NAC should be continued beyond the usual course of therapy in any patients with sign of liver injury and discontinue when aminotransferase activities that have peaked and are improving, a normal prothrombin time/INR (< 1.3) and no acidosis [70].

By following way we can manage the acute paracetamol overdoses.

(1) Plot the paracetamol concentration onto Rumack-Mattew nomogram. If the level will not return before 8 hours from the time of ingestion, begin NAC pending the level.

(2) If the level plots above the 150 μg/mL treatment line, begin NAC.

(3) If NAC is administered IV, repeat the paracetamol level and measure the serum AST and ALT before completion of NAC.

   a. May discontinue NAC if paracetamol level is < 10 μg/mL and serum AST and ALT are not increased more than the references range and increasing.

   b. If paracetamol is > 10 μg/mL or either serum AST or ALT are elevated, continued NAC until paracetamol is less than 10 μg/mL and AST and ALT have peaked and are improving.

Table 3: Managements of Acute paracetamol overdose [68].

Oral NAC has unpleasant taste, smell and vomiting is common. Nausea and vomiting can be reduced by diluting the NAC with soda, holding one breath while taking the medication or administering by nasogastric tube. Eventually about 5 % of patients may not tolerate oral NAC and require IV therapy. Anaphylactoid reactions (e.g. Rash, itching, angioedema, bronchospasm, tachycardia and hypotension) develop in 10-20% of patients treated with IV NAC [75, 76]. Patients with flushing alone or mild symptoms do not require intervention and the infusion can be continued with careful monitoring. Patients who develop urticaria, angioedema, hypotension and bronchospasm should be treated with one or more medications of diphenhydramine, corticosteroids and bronchodilators. The infusion should be stopped and can be restarted at slower rate with close monitoring [77]. IV regimen is preferred for patients with ALF and who's who refuse or has a contraindication to oral administration (coma, pancreatitis, bowel ileus or obstruction).

Treatment failure after the standard IV course of NAC have occurred after massive ingestion and after a overdoses that included a co-ingestant that slow GI motility, such as anticholinergic drugs or opoids drugs. In this condition, either paracetamol was present or sign of hepatic injury were evident at the completion of the 21 hours course of IV NAC [78-80]. If paracetamol is still detectable or there are sign of hepatic injury, NAC

should be continued until paracetamol is not detected and if there were any sign of hepatic injury, these parameters were also improving. In this setting, NAC continue at a rate of 6.25mg/kg/h.

For patients who presents after repeated supratherapeutic ingestion, assessment should include a serum paracetamol level, aminotransferase level and prothrombin time/INR. If paracetamol was > 10 μg/mL or aminotransferase was increased more than normal range, NAC was started. NAC was continued until the paracetamol level was less than 10 μg/mL and aminotransferase had peaked and were either static or decrease. The management described by Daley and Colleagues is very reasonable approach to patients seen with a history of repeated excess ingestion, table-3[81].

By the following way, we can manage.
(1) Obtain the serum APAP, AST and ALT levels.
(2) If a paracetamol level is < 10 μg/mL, AST and ALT levels are normal, no treatment is necessary.
(3) If paracetamol level is > 10 μg/mL or either AST or ALT Levels elevated more than references ranges, begins NAC treatment.
(4) Continue NAC until paracetamol level is < 10 μg/mL and the AST and ALT have peaked and are improving and there is no other sign of hepatic dysfunction, including INR of 1.3 or less.

Table 4: management of repeated supratherapeutic ingestion [81]

Liver transplantation:

Liver transplantation is lifesaving in those paracetamol overdose patients who progress to severe FHF. Several prognostic parameters or criteria have been identified to facilitate the decision making to need for the LT. The most widely used prognostic criteria are those of king college hospital. These criteria developed in the 1980 from a large cohort of patients with paracetamol hepatotoxicity. The criteria are either arterial PH less than 7.30 after fluid resuscitation or combination of an INR greater than 6.5 plus serum creatinine greater than 3.4 mg/dL and grade III or IV encephalopathy(Stupor, coma)[54]. These criteria, although not very sensitive, had a high specificity in identifying patients who would do poorly without transplant. Less than 20% of those who met the KCH criteria survived spontaneously [49]. A modification to these criteria added blood lactate measured 2 to 3 days after acute overdose. A lactate level on days 2 to 3, > 3.5 mmol/L before adequate fluid resuscitation or > 3 mmol/L after patients have been adequately fluid resuscitation was predictive of death without liver transplant. This modification improved both sensitivity and specificity of the KCH criteria [82].A serum phosphate > 1.2 mmol/L at 48 to 96 hours after overdose was predictive of death [101][83].

The model of End stage liver disease (MELD) score has been investigated with paracetamol hepatic injury. Component of the MELD score are INR, serum bilirubin, serum creatinine and causes of liver injury. In a group of patients with paracetamol hepatotoxicity, a higher MELD score on admission to the ICU was associated with progression to encephalopathy and an increase in the MELD score over the first days after onset of hepatic encephalopathy was predictive of death. The acute physiology and chronic health evaluation II score has been used to predict death from paracetamol hepatotoxicity. A score of more than 15 on admission

to the ICU was a sensitive to predict patients likely to progress to FHF and was slightly more sensitive than KCH criteria on the days of admission [84].

A critical decision for clinicians is the decision to refer patients to a specialized liver unit. Criteria to consider in this section include acidosis, renal insufficiency, Prothrombin time, INR > 5, hypoglycemia or encephalopathy [84]. An increase in the INR from day 3 to 4 after overdoses has been associated with a poor outcome [85].

Other treatment modalities:

Several biological agents such as inducible protein-10, macrophage inducible protein-2, interleukin-6, -11,-22 and interferon have been demonstrated to decrease susceptibility for paracetamol toxicity in experimental models [86, 87]. Telmisartan [88] and coenzyme Q 10[89] can alleviate oxidative stress injury associated with paracetamol in animal's models. However to our knowledge, none of these agents have come to the clinical phase of study.

CONCLUSIONS

Paracetamol toxicity is the most common cause of acute liver failures. With early recognition and administration of NAC within 8 hours, following an acute overdose, serious toxicity can be prevented. With massive ingestions and polypharmacy overdose, there may be prolonged absorption of paracetamol with measurable level of paracetamol still present at the completion of standard course of IV NAC. NAC should not be discontinued until there is no further paracetamol to metabolize and any signs of liver injury are improving. In addition to the antidotal properties of early treatment with NAC to prevent the production of toxic metabolite, NAC also beneficial in the treatment of paracetamol induced hepatic injury and should be used in patients with late presentation and sign of hepatic injury. Patients with FHF require expert management and are best served by transfer to specialized liver unit with transplant capability.

Abbreviations:

NAPQI: N-acetyl-Para-benzoquineone imines.

CYP: Cytochrome p-50

FHF: Fulminant hepatic failure.

ALT: Alanine aminotransferase.

AST: Aspartate aminotransferase.

INR: International normalized ratio.

ARF: Acute renal failure.

PT: Prothrombin time.

NAC: N-acetylcysteine.

KCH: King college criteria.

MELD: Model for end stage liver disease.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

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