Review Article

All drugs are poisons at a higher dose - acute paracetamol poisoning

S. Palaian, P. R. Shankar, R. Paudel, M. Prabhu, P. Mishra

Department of Hospital and Clinical Pharmacy, Department of Pharmacology, Department of Medicine, Manipal Teaching Hospital / Manipal College of Medical Sciences Pokhara, Nepal; Department of Medicine Kasturba Hospital/ Kasturba Medical College Manipal, Karnataka, India.
Correspondence to: S. Palain, Department of Hospital and Clinical Pharmacy, Manipal College of Medical Sciences, Pokhara

Paracetamol is considered to be a safe and effective drug and is available over the counter in many countries including Nepal. Though it is considered safe at its therapeutic dose, it may be toxic at higher dose. It is recognized as a major drug leading to poisoning in the United States of America, United Kingdom and even in Nepal. Several factors such as age of the patients, sex, alcohol intake, disease conditions, concomitant drug intake etc are known to be important factors affecting the severity and outcome of the poisoning. The signs and symptoms are exhibited in a sequential manner and may start with mild nausea and may end with fulminant hepatic failure. Though paracetamol poisoning is associated with many complications and may affect the cardiovascular, respiratory and renal systems, hepatotoxicity is the major complication leading to death. Since paracetamol may be available in combination with other drugs, on many occasions the patient may not present with classical symptoms of paracetamol poisoning. Several laboratory investigations along with the patients' signs and symptoms help in diagnosis. The management involves symptomatic treatment and a specific antidote mainly N-acetyl cysteine. The estimation of plasma paracetamol concentration is beneficial in diagnosing as well as monitoring the poisoned patient. The pattern and management of paracetamol poisoning varies with the patient populations such as pregnant women, pediatric patients etc. Several strategies including restriction of pack size have been implemented worldwide to prevent the occurrence of paracetamol poisoning. Availability of unbiased drug information is very much essential in management.

Introduction

Paracetamol is a safe and effective drug that is commonly used and in many countries it is available as over the counter (OTC) preparation and hence dispensed by the pharmacist without a prescription[1]. The United States Food and Drug Administration (US FDA) has approved paracetamol for the management of common cold, dysmennorhea, head ache, fever and pain[2]. Because of its safety profile and cost, it is one of the preferred drugs and is used as a house hold remedy. In Nepal paracetamol is available as tablets, pediatric drops and suspension and as injection. It is available in combination with various other drugs. Because of its wide spread use and availability, it is known to be one of the important causes of drug induced poisoning; both accidental as well as suicidal. The authors in this review article aim to provide an overview of paracetamol poisoning, its management and strategies to prevent the occurrence of the same.

Epidemiology of paracetamol poisoning: Paracetamol is the commonest drug taken in overdose in the United Kingdom (UK) accounting for 48% of all hospitalizations due to poisoning [3]. Paracetamol overdose is the commonest cause of acute liver failure in the UK, accounting for at least half of all cases sent to tertiary referral units [4].

In the United States (US), paracetamol alone accounted for 4.1% of deaths from poisoning reported to American poisons centers in 1997[5]. In the US, it is considered as the second leading cause of toxic drug ingestions[6]. In Singapore, paracetamol is responsible for one half of all deliberate self poisoning among the young people[7]. A recent study from Patan Hospital, Kathmandu, Nepal has reported paracetamol as one of the most frequently used drug responsible for poisoning [8].

The cause of poisoning may be accidental or deliberate. Data from Western countries suggest the cause to be deliberate in majority of cases. Retrospective data from an American hospital identified 14% of ingestions as accidental and 86% as deliberate[9]. Data from the Accident and Emergency Department at Guy's Hospital, London shows 16% of poisonings were accidental and the remaining were intentional[10]. We could not locate the local data in this regard.

Factors affecting the severity and outcome of paracetamol poisoning: The various factors affecting the severity and outcome of paracetamol poisoning can be broadly classified as patient related (mainly age) and drug related factors (mainly intake of concomitant medications). These factors are discussed below.

1. Age: In acute exposure, mortality and morbidity are decreased in pediatric patients compared to adults. Whether this difference is due to age-related differences in metabolism, increased glutathione stores, or low ingested doses is unclear[7]. However children younger than 10-12 years of age appear to be less susceptible to hepatotoxicity because of the smaller contribution of cytochrome P450 to paracetamol metabolism[11]. The role of cytochrome P 450 is vital since the metabolite produced by this enzyme is responsible for hepatotoxic effects, the major cause of death.

2. Concomitant medications: The use of concomitant medications contributes to hepatotoxicity by stimulating the cytochrome P450 enzyme system as well as by synergistic hepatotoxic effects. In a case series of 737 patients admitted to the hospital with paracetamol poisoning, 332 patients also took other regular medication regularly. A multivariate analysis determined that co-medication with opioid analgesics was associated with a significantly higher risk of hepatic dysfunction, confirmed by logistic regression analysis. This may be due to depletion of hepatic glutathione. Other medications (psychotropics, analgesics, oral contraceptives, beta-agonists or anticonvulsants) were not reported to affect the outcome of the paracetamol overdose [12].

Paracetamol overdose in patients on long-term anticonvulsant therapy was associated with increased mortality and a trend toward more severe coma, acidosis and coagulopathy when compared with overdose patients not taking anticonvulsants in a retrospective study[13].

3. Miscellaneous: Alcohol intake is associated with increased risk of hepatotoxicity[14]. Some patients with Gilbert's disease may be predisposed to develop paracetamol induced hepatotoxicity[15]. The severity of paracetamol poisoning is enhanced by starvation and fasting. Some evidence suggests that fasting lowers the threshold for hepatotoxicity from paracetamol [16].

Pharmacokinetic profile of paracetamol:[17,18] Paracetamol is rapidly absorbed in therapeutic doses, with peak levels reached in 1-2 hours and 2-4 hours in the overdose setting. Therapeutic levels range from 10-20 mcg/ml. Protein binding is around 10%, with a volume of distribution of 0.9 l/kg. Metabolism is primarily hepatic; the half-life is 2-4 hours.

Signs and symptoms: [11,18-22] The **c**linical symptoms and signs of the patients following paracetamol overdose can be divided into 4 phases.

Phase 1: This phase occurs within several to 24 hours after ingestion. Characteristic features include anorexia, nausea, and vomiting.

Phase 2: This phase occurs 24 to 48 hours after ingestion, and during this period symptoms may improve transiently. Evidence of hepatic injury becomes apparent as transaminase and bilirubin levels and prothrombin time (PT) begin to increase. Right-upper-quadrant pain and hepatomegaly may be present, and oliguria secondary to dehydration or acute tubular necrosis may be noted.

Phase 3: There is some natural overlap between phases, with phase 3 lasting from 72 to 96 hours after ingestion. Nausea and vomiting may reappear or worsen. Malaise, jaundice, and central nervous system symptoms (eg, confusion, somnolence, coma) may be seen. During this phase, liver function abnormalities reach a peak. The aspartate aminotransferase (AST) level may exceed 10,000 IU/l, the alanine aminotransferase (ALT) level usually reaches more than 1,000 IU/l, PT may be greater than 2.2 times the control value, and bilirubin level may approach 4 mg/dl.

Phase 4: This phase usually begins 6 or 7 days after ingestion and is characterized in most cases by resolution of hepatic damage. Abnormal laboratory values begin a steady return to normal. Patients who do not recover at this point may progress toward fatal hepatic failure, which is the outcome in 1% to 2% of untreated patients who have a plasma paracetamol level in a toxic range.

Complications: [11,18,23-26] The major complications associated with paracetamol poisoning are related to the liver. Apart from the hepatic effects, other vital organs are also affected. However, it is rare and usually mild in nature. The various complications due to paracetamol poisoning are discussed below.

1. Liver: Main organ affected in paracetamol overdose is liver and it is a cause of death. Paracetamol causes a dose-related toxicity resulting in centrilobular necrosis. Paracetamol normally undergoes the phase 2 reactions of glucuronidation and sulphation. However it is metabolized by Cytochrome P450 2E1 to N-acetyl-p-benzoquinoneimine (NABQI) if the capacity of the phase 2 reactions is exceeded or if cytochrome P450 2E1 is induced. After normal doses of paracetamol, NABQI is detoxified by conjugation with glutathione to produce mercaptopurine and cysteine conjugates. Following overdose, tissue stores of glutathione are depleted allowing NABQI to accumulate and cause cell damage. Illness, starvation and alcoholism deplete glutathione stores and increase the risk of hepatotoxicity.

2. Cardiovascular system: Myocardial injury with ECG changes and CPK MB elevation has rarely been reported in severe overdose. It is unclear if paracetamol is a direct myocardial toxin or if these effects are secondary to metabolic or cardiopulmonary abnormalities induced by severe paracetamol toxicity.

3. Respiratory system: In a retrospective study of 24 patients with hepatic failure following paracetamol poisoning, 8 developed severe lung injury and 1 mild to moderate injury. Patients with pulmonary injury were more likely to have increased intracranial pressure and circulatory failure, had more severe hepatic coma scores on admission and had a higher mortality rate than did patients without lung injury [(8 of 9 (89%) vs 2 of 15 (13%)] [27].

4. Effects on temperature: Hypothermia is reported commonly during acute paracetamol poisoning.

5. Gastrointestinal effects: Nausea and vomiting may develop soon after ingestion and may recur 12 to 24 hours later with the onset of abdominal pain and hepatotoxicity. Hyperamylasemia is common, although clinical signs of pancreatitis may not be obvious.

6. Nephrotoxicity: Nephrotoxic effects include acute tubular necrosis, flank pain, hematuria, proteinuria, and an antidiuretic hormone effect.

7. Metabolic complications: Metabolic acidosis and high blood lactate levels may be seen early (12 hours), especially in severe overdose. Metabolic acidosis is common 3 to 4 days after ingestion in patients developing hepatic failure. Hyperglycemia is rare and may represent laboratory interference. Hypoglycemia may be seen 2 to 4 days after overdose associated with hepatic failure. The patients can also present with bleeding disorders.

Diagnostic methods and monitoring parameters for paracetamol poisoning: [11,19,22,26,28] Co ingestion of other drugs or use of combinations can make the diagnosis very difficult. Prompt diagnosis is possible only if the ingestion is suspected and a serum paracetamol level obtained. However, patients may fail to provide the history of paracetamol ingestion, because they are unable (eg comatose from other co ingested substances), unwilling or unaware of its importance. Due to this problem it may be advisable to check the blood paracetamol levels. However, facilities for estimating the serum paracetamol level are limited in Nepal.

Serum estimation should be done between 4 and 24 hour after ingestion. Determinations performed prior to this time are not reliable for assessing potential hepatotoxicity. Initial plasma concentration above 150 mcg/ml at 4 hrs, 100 mcg per ml at 6 hrs, 70 mcg per ml at 8 hrs, 50 mcg per ml at 10 hrs, 20 mcg per ml at 20 hrs, or 3.5 mcg per ml at 24 hrs post ingestion indicate possible hepatotoxicity and the need for completing the course of NAC treatment. The paracetamol toxicity nomogram (Rumack-Matthew Nomogram) [29] can be followed for assessing the possible hepatotoxicity and the need for antidote therapy.

In patients with toxic paracetamol levels, determine SGOT (AST), SGPT (ALT), total bilirubin and INR (or PT) on admission and daily for 3 days or until levels begin to return to normal. If significant abnormalities in liver function develop, creatinine, Blood Urea Nitrogen (BUN), urinalysis, electrolytes, glucose, hemoglobin, hematocrit, amylase and ECG should be followed as clinically indicated.

Renal insufficiency may develop 2 to 4 days after toxic ingestion, peak levels of BUN and creatinine may be delayed by 7 to 10 days. Generally renal and hepatic toxicity develop concurrently; rarely renal injury develops alone. Hyperphosphatemia (greater than 1.2 mmol/l), occurring 48 to 96 hours after the overdose, and in the presence of both renal and hepatic dysfunction, is a poor prognostic indicator. The monitoring parameters for acute paracetamol poisoning are determination of plasma paracetamol concentration between 4 and 24 hours, carrying out the AST/ALT estimation, prothrombin time and bilirubin time at 24-hour intervals for at least 96 hours post ingestion. The abnormal

value of this test indicates potential hepatotoxicity. If abnormalities are not observed after 96 hours, further determinations are not needed.

Therapeutic and toxic dosages of paracetamol: The therapeutic dose of paracetamol for various indications is shown in Table 1.

Table 1. Therapeutic dose of paracetamol

Indications		Dosage regimen
Adult	Fever	650-1000 mg orally every 4 hrs as needed, maximum 4 g/day
		650 mg rectally every 4-6 hrs; maximum 6 suppositories/24 hrs
	Pain (Mild to Moderate)	650-1000 mg orally every 4 hrs as needed, maximum 4 g/day
		650 mg rectally every 4-6 hrs; maximum 6 suppositories/24 hrs
Pediatric	Fever	10-15 mg/kg/dose orally every 4-6 hrs, maximum 5 doses/day
		Age 6-12 yrs, 325 mg orally every 4-6 hrs, maximum 2.6 g/24 hrs
		Age 3-6 yrs, 120-125 mg rectally every 4-6 hrs; maximum 720 mg/24 hrs
		Age 1-3 yrs, 80 mg rectally every 4 hrs
		Age 3-11 months, 80 mg rectally every 6 hrs
	Pain (Mild to Moderate)	10-15 mg/kg/dose orally every 4-6 hrs, maximum 5 doses/day
		Age 6-12 yrs, 325 mg orally every 4-6 hrs, maximum 2.6 g/24 hrs
		Age 3-6 yrs, 120-125 mg rectally every 4-6 hrs; maximum 720 mg/24 hrs
		Age 1-3 yrs, 80 mg rectallly every 4 hrs
		Age 3-11 months, 80 mg rectally every 6 hrs

The toxic dose of paracetamol is listed in Table 2.

Management: [11,18,23,28] The management of paracetamol poisoning is mainly targeted at preventing the occurrence of hepatotoxicity. Apart from the management of hepatotoxicity symptomatic measures are instituted based on the clinical symptoms of the patients.

1. Decreasing absorption: It can be done by emptying the stomach via induction of emesis or gastric lavage. Gastric lavage should be limited to patients with a recent (within 60 min) and potentially life-threatening toxicity.

Inducing prolonged emesis by using ipecac may interfere with N-acetyl cysteine (NAC) administration. In patients with deliberate overdose and in children with accidental ingestion of a sufficient amount to require evaluation at a medical facility, activated charcoal is preferred over ipecac for gastric decontamination *(Table 3)*.

Activated charcoal adsorbs paracetamol, but its use has been controversial since it also adsorbs some amount of NAC thus reducing its efficacy as an antidote. Despite this NAC is used in combination with activated charcoal based on the clinical condition.

2. Enhancing elimination: Instituting hemodialysis or hemoperfusion to remove the paracetamol from the circulation may be beneficial if NAC administration cannot be instituted within 24 hours following ingestion of huge amounts of paracetamol. However, the effectiveness of this method is unknown.

3. Use of antidotes: It is recommended to use NAC as soon as possible after ingestion of an overdose. It should be given without waiting for the plasma paracetamol estimations or other laboratory investigations. NAC is beneficial if started within 10-12 hrs of ingestion. However, it may offer some benefits even if given within 24 hours.

NAC provides benefit in four ways. It is converted to cysteine, which can replenish the depleted glutathione stores. It also directly detoxifies the toxic NABQI to nontoxic metabolites. It can also provide a substrate for sulfation, thereby increasing the capacity for nontoxic metabolism. NAC can also directly conjugate NABQI to reduce toxicity.

Usually NAC is given orally. However, intravenous NAC is recommended for selected patients, including those with gastrointestinal bleeding or obstruction, potential fetal toxicity from maternal toxicity, or an inability to tolerate oral NAC. Moreover, NAC induces vomiting which is again aggravated by the toxic dose of paracetamol. So intravenous NAC is preferred. An antiemetic such as metoclopramide or ondansteron may be needed to control the vomiting.

Supportive treatment: It includes maintaining fluid and electrolyte balance, correcting hypoglycemia and administering Vitamin K and fresh frozen plasma. Patients with intentional overdose should be referred to a Psychiatrist and should be thoroughly counseled.

5. Liver transplantation: If the patient develops irreversible hepatic failure, then the patient can be referred for liver transplantation. The possible criteria for liver transplantation include metabolic acidosis, renal failure, coagulopathy, and hepatic encephalopathy. One of the most widely accepted criteria for liver transplantation is provided by the Kings College hospital, London[30]. It is as follows: blood pH <7.3 (irrespective of grade of encephalopathy) or Prothrombin time >100 sec (INR > 7.7) and serum creatinine >300 mmol/L (>3.4 mg/dL) in patients with grade III or IV encephalopathy.

Table 3. Profile of drugs used in paracetamol poisoning

Antidote	Dose	Pediatric dose	Contraindication/Precautions	Side effects	Interactions	Pregnancy category
N-acetyl cysteine	Oral dose: 140 mg/kg orally once, followed by 70 mg/kg orally q4h for 17 doses IV dose 150 mg/kg over 15 mins followed by 50 mg/kg in 500 ml of dextrose 5% in the next 4 hours and 100 mg/kg in 1000 ml of 5% dextrose in the next 16 hours	Similar to that of adult dosage	Documented hypersensitivity	Nausea, vomiting; diarrhea, headache, urticaria, and hypotension IV injection may cause anaphylactic reaction	-	B *
Activated charcoal	50-60 g orally as a single dose	1 g/kg oral as a single dose	Documented hypersensitivity	Nausea, vomiting, and possible aspiration in an unprotected airway; stools turns back	May inactivate ipecac syrup if used concomitantly. Do not mix charcoal with sherbet, milk, or ice cream (decreases adsorptive properties of activated charcoal)	C **
Ipecac	30 ml orally followed by 8 or more ounces (1 ounce= 30 ml) of water	Less than 1 year 1 to 2 teaspoonful (5 to 10 milliliters). -1 year or older 3 teaspoonful (15 milliliters).	Cardiovascular conditions	Diarrhea, Stomach cramps Lethargy	-	Unknown

Notes: 1) If vomiting does not occur within 20 minutes with Ipecac, a similar dose is repeated once. If the patient does not vomit within 30 minutes, the dosage should be recovered by gastric lavage

2) The dose of oral NAC should be repeated if the patient develops vomiting with in one hour of NAC administration.

*** (Category B)** - Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women or Animal studies have shown an adverse effect on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.

**** (Category C)** - Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, or No studies are available in either animals or pregnant women.

Acute paracetamol poisoning in special populations: The pattern of paracetamol poisoning may differ in special patient populations such as pregnant women, Acquired Immune Deficiency Syndrome (AIDS) patients and in children.

1. Pregnant women: Pregnant acute overdose patients have delivered normal healthy infants [31,32]. Paracetamol appears to cross the placenta, and fetal liver cells are capable of metabolizing paracetamol, placing the fetus at risk in overdose. Paracetamol overdose does not appear to increase the risk for birth defects or adverse pregnancy outcome unless severe maternal toxicity results [33]. Pregnant overdose patients with toxic paracetamol levels should be treated with NAC as soon as possible after the overdose and delivery should not be induced before the protocol is completed unless there are other overriding factors. Rapid treatment with NAC of the pregnant patient is the best way to treat the fetus.

In a series of 4 pregnant women with paracetamol overdose who delivered their infants while receiving NAC therapy, none of the infants had evidence of paracetamol toxicity, while two of the mothers developed hepatotoxicity, one did not and results of the fourth mother were unknown. NAC appears to cross the human placenta and may provide protection from paracetamol toxicity in the infant[34].

2. In AIDS patients:[18] Patients with AIDS may have nutritionally related depletion of glutathione. Multiple doses of paracetamol should be probably avoided in Zidovudine (the drug commonly included in the (Highly Active Antiretroviral Therapy) HAART regimen) treated patients who are suspected of having diminished stored glutathione due to poor nutrition, AIDS or alcohol consumption.

3. In children: Children are more resistant to paracetamol induced liver damage than adults [35]. However, chronic over dose is more likely to result in harm than acute ingestion. Special care should be taken with children who are malnourished or on cytochrome P450 enzyme inducing drugs. Toxic paracetamol concentrations associated with the accidental ingestion of paracetamol suspension are extremely rare. A careful history can often obviate the need for investigation or treatment. The volume, and paracetamol concentration, of the formulation should be established from the packaging [36].

If the potential dose of paracetamol consumed can be established with absolute certainty as being below 150 mg/ kg, no further action is required. Where deliberate ingestion is reported or suspected, or the dose accidentally ingested cannot be confirmed, the blood paracetamol concentration should be measured. Paracetamol must be measured only after four hours following ingestion. As already said, samples taken prior to this may be unreliable because of the possibility of continuing absorption and changing drug distribution [36]. In malnourished children and children with low body weight, the risk of toxicity is high.

Strategies to prevent the occurrence of paracetamol poisoning: Several strategies were implemented to minimize the occurrence of paracetamol poisoning with varying degree of success. Some of the commonly employed strategies are discussed below.

1. Reducing the pack size: The legislation to limit the pack size of paracetamol was introduced in the UK in September 1998. The legislation mentions that pharmacies can sell a maximum of 32 tablets per sale (previously there was no limit), although they can still sell up to 100 tablets in justifiable circumstances Other retail outlets can sell a maximum of 16 tablets (the previous limit was 24) Specific warnings of the dangers of paracetamol overdose are now printed on packets and on leaflets in packets A study in the UK concluded that legislation restricting pack sizes has had substantial beneficial effects on mortality and morbidity associated with self poisoning using these drugs [37].
In Nepal, paracetamol is available in different formulations *(Table 4)*. The preparations are not restricted by the licensing authorities and are easily available from a retail pharmacy.

Table 4. Paracetamol preparations available in Nepal

Dosage form	Concentration
Suspension (50 ml)	125 mg/5 ml
Suspension (60 ml)	Paracetamol 125 mg/ Ibuprofen 100 mg/ml
	Paracetamol 162.5 mg/ Ibuprofen 100 mg/ml
Drops (15 ml)	150 mg/ml
	75 mg/ml
Tab (Plain)	Paracetamol 500 mg
	Paracetamol 500 mg+Codeine 10 mg
Tab (Combination)	Paracetamol 500 mg+Caffeine 25 mg
	Paracetamol 500 mg+Chlorzoxazone 250 mg
	Paracetamol 500 mg+Ibuprofen 400 mg
	Paracetamol 500 mg+Phenylephrine 5 mg+ Chlorpheneramine 2 mg
	Paracetamol 500 mg+Codeine sulphate 10 mg
Inj (2 ml)	Paracetamol 150 mg /ml

2. Patient education and counseling: The healthcare workers should educate the parents on the proper dose of paracetamol based on weight and inform them that various preparations have different concentrations of paracetamol. They should be also made aware that many cold and cough products also contain paracetamol and hence they should

read labels carefully [17].

Patients who purchase preparations containing paracetamol should be made aware of the danger of overdosing which may occur if they take other paracetamol containing preparations simultaneously. Patients and their care givers should be helped to recognize signs of hepatotoxicity and report immediately symptoms like malaise, nausea, fever, and abdominal discomfort [38].

3. Poison information centers: Poison information centers play an important role in management. They can develop simple charts for the management of paracetamol poisoning. The charts may be distributed to the healthcare members as well as the emergency departments. They can also prepare the treatment guidelines for paracetamol poisoning based on the local pattern of the poisoning, keeping in mind the availability of the drugs used in management .

4. Patient information leaflets: The patient information leaflets should also mention the possibility of overdose due to paracetamol and should state a warning regarding the toxicity of paracetamol.

Conclusion: Paracetamol, one of the most commonly used effective, economic drugs is definitely a safe drug when used at therapeutic doses. However, in predisposed patients when taken at high doses, paracetamol can be potentially toxic. Since the toxic dose of paracetamol is not substantially different from its therapeutic dose, education of the patient and parents (in case of pediatric patients) is necessary. If poisoning occurs, the patient should be hospitalized and treated aggressively like any other potentially fatal poisoning.

References

1. Routledge P, Vale JA, Bateman DN et al. Paracetamol (acetaminophen) poisoning. No need to change current guidelines to accident departments. *Br Med J*. 1998; **317:**1609-10.
2. Acetaminophen In: Klasco RK (Ed): *DRUGDEX® System*. Thomson Micromedex, Greenwood Village, Colorado (Edition expires [3/2006]).
3. Wallace CI, Dargon PI, Jones AL. Paracetamol overdose: an evidence based flowchart to guide management. Emer Med J 2002; 19:202-5.
4. Bray GP. Liver failure induced by paracetamol. *Br Med J*. 1993; **306:**157-8.
5. Litovitz TL, Klein-Schwartz W, Dyer KS, Shannon M, Lee S, Powers M. 1997 Annual report of the American association of poison control centers toxic exposure surveillance system. *Am J Emerg Med.* 1998; **16**: 443-97.
6. Litovitz TL, Holm KC, Clancy C, Schmitz BF, Clark LR, Oderda GM. 1992 annual report of the american association of poison control centers toxic exposure surveillance system. *Am J Emerg Med.* 1993; **11:** 494-555
7. Mohd ZZ, Fathelrahman AI, Ab Rahman AF. Characteristics and outcomes of paracetamol poisoning cases at a general hospital in Northern Malaysia. *Singapore Med J*. 2006; **47:**134-7
8. Poudyal BP. Poisoning: Pattern and profile of admitted cases in a hospital in central Nepal. *J Nep Med Assoc*. 2005; **44:** 92-6.
9. Gyamlani GG, Parikh CR. Acetaminophen toxicity: suicidal vs accidental. *Crit Care*. 2002; **6: 155–**9.
10. Dargan PI, Ladhani SL, Jones AL. Measuring paracetamol concentrations in all patients with drug overdose or altered consciousness: does it change outcome? *Emerg Med J*. 2001; **18:** 178–82.
11. Olson KR. Acetaminophen. In: Olson KR, eds. *Poisoning and drug overdose.* 3rd edition, Connecticut: Appleton and Lange, 1998: 62-5.
12. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in paracetamol-induced hepatotoxicity. *Hepatol*. 2002; **35:** 876-82.
13. Bray GP, Harrison PM, O'Grady JG. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. *Human Exp Tox*. 1992; **11:** 265-70.
14. Whitcomb DC, Block GD. Association of paracetamol hepatotoxicity with fasting and ethanol use. *JAMA*. 1994; **272:** 1845-50.
15. Esteban A, Perez-Mateo M. Gilbert's disease: a risk factor for paracetamol overdose? (letter). *J Hepatology*. 1993; **18:** 257-8.
16. Whitcomb DC, Block GD. Association of paracetamol hepatotoxicity with fasting and ethanol use. *JAMA*. 1994; **272:**1845-50.
17. Tucker J. Toxicity, *Paracetamol*. emedicine. Available on http://www.emedicine.com/ ped/topic7.htm (Accessed on 23rd February 2006)
18. Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J, eds. *Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning.* 2nd ed. Baltimore: Williams and Wilkins, 1997:180-95
19. McEvoy GK, Miller J, Litvak K et al editors. *AHFS Drug Information.* United States of America: American Society of Health-System Pharmacists; 2003. ISBN 1-58528-039-9
20. Larsen LC, Fuller SH. Management of paracetamol toxicity. *Am Fam Physician*. 1996; **53:**185-90
21. Luria JW, Ruddy R, Stephan M. Acute hepatic failure related to chronic paracetamol intoxication. *Pediatr*

Emerg Care. 1996; **12 :** 291-3.
22. Chyka PA. Clinical toxicology. In: Dipirio JT, Talbert RL,Yee GC, Mattzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy A pathoplysiological approach.* 6th ed. Connecticut: Appleton and Lange;2005; 125-48.
23. *British national formulary.* 50th edition, British medical association, London; 2005.
24. Sweetman SC. Editor. *Martindale The Complete Drug Reference.* 33rd edition. London, Pharmaceutical Press; 2002.
25. Roberts LJ, Morrow JD. Analgesics-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. *Goodman and Gilman's The Pharmacological basis of therapeutics.* Hardman JG, Limbard LE, eds. 10th ed, Mc Graw-Hill: New York, 2001, 687-731.
26. Linden CH, Burns MJ. Poisoning and drug overdose. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 15 th edition, United States of America: McGraw-Hill, 2001; 2595- 616.
27. Baudouin SV, Howdle P, O' Grady JG. Acute lung injury in fulminant hepatic failure following paracetamol poisoning. *Thorax*. 1995; **50:** 399-402.
28. Drug information for the healthcare professional. *USPDI* 24th edition, Volume I, 2004, Thomson Micromedex, USA.
29. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; **55:** 871-6.
30. O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology.* 1989; **97:** 439-45
31. Byer AJ, Traylor TR, Semmer JR.. Paracetamol overdose in the third trimester of pregnancy. *JAMA.* 1982; **247:** 3114-5.
32. Ludmir J, Main DM, Landon MB. Maternal paracetamol overdose at 15 weeks of gestation. *Obstet Gynecol.* 1986; **67:** 750-1.
33. Kozer E, Koren G. Management of paracetamol overdose. Current controversies (review). *Drug Safety*. 2001; **24:** 503-12.
34. Horowitz RS, Dart RC, Jarvie DR. Placental transfer of N-acetylcysteine following human maternal paracetamol toxicity. *Clin Toxicol*. 1997; **35:** 447-51.
35. Rumack BH, Peterson RG. Paracetamol overdose: incidence, diagnosis, and management in 416 patients. *Pediatrics*. 1978; **62** (5 pt 2 suppl): 898–903.
36. Riordan M, Rylance G, Berry K. Poisoning in children 2: Painkillers. *Arch Dis Child.* 2002; **87:** 397-9.
37. Hawton K, Townsend E, Deeks et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. *Br Med J*. 2001; **322:** 1–7.
38. Cadman BE, Featherstone B. Adverse effects of drugs on the liver. In: Walker R, Edwards C, eds. *Clinical Pharmacy and Therapeutics.* 3rd edition. Philadelphia: Churchill Livingstone, 2003; 843-52.