



## METABOLIC ACIDOSIS VS TRANSAMINASES LEVEL IN DIAGNOSIS AND PREDICTING PROGNOSIS OF ACETAMINOPHEN POISONING

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### ABSTRACT

Background: Paracetamol (APAP) is the most famous drug used in the world to relieve of pain and used as an antipyretic. Paracetamol overdose induces liver damage and is a well known hepatotoxic drug. This study was aimed to determine the incidence of acidosis in acetaminophen overdose with the time of N- Acetyl Cystiene (NAC) administration and correlation of late acidosis and death in acetaminophen overdose. Materials and methods: The data were obtained from the patients' files admitted to AL-Noor Hospital due to the ingestion of Paracetamol overdose. The Data on Paracetamol levels, liver transaminases (AST, and ALT), arterial blood gases, lactate levels and serum electrolyte levels had been collected from files. Results: Fifty five cases were divided into three groups: Group I (33 cases) had early acidosis with toxic APAP dose; Group II (9 cases) had late acidosis with toxic APAP dose; and Group III (13 cases) with non toxic APAP ingestion or developed acidosis. In 65.45% of cases, the age was between 14-30 years. Most of the cases were females (74.5%), and the adult was 78.77% while 21.23% were children. There was a positive significant relation ( $P < 0.05$ ) Between APAP toxic doses, early NAC administration, early anion gap acidosis and complete recovery. Also, there was a positive significant relation ( $P < 0.05$ ) between, APAP toxic doses, late NAC administration, late lactic acidosis with coma and death. There was no significant relation ( $P > 0.05$ ) between serum transaminases and toxic APAP level or prognosis. Conclusion: Metabolic acidosis are a specific indicator for APAP hepatotoxicity than serum transaminases

**KEY WORDS:** Paracetamol overdose, Metabolic acidosis, APAP hepatotoxicity



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## INTRODUCTION

Acetaminophen (paracetamol) is a mild analgesic antipyretic agent, which is used frequently worldwide<sup>(1, 2)</sup>. Paracetamol (APAP) overdose can result in severe hepatotoxicity. In general, a single dose of 150 mg/kg or more may produce acute liver failure characterized by centrilobular necrosis both in human and experimental animals<sup>(3)</sup>, but smaller doses may also cause liver damage<sup>(4)</sup>. Currently, paracetamol overdose is the leading cause of liver cell failure (LCF) in the United States, Great Britain and most of the European Countries. It accounts for approximately 50% of all cases of the acute LCF in the United States and carries a 30% mortality<sup>(5)</sup>. APAP hepatotoxicity has been attributed to the metabolic activation of acetaminophen to a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) in the liver by cytochrome p450 isoenzymes especially CYP2E1<sup>(6)</sup>. NAPQI reportedly depletes liver glutathione thereby inducing oxidative stress. It also binds to vital cellular and mitochondrial proteins leading to cellular necrosis, and may activate cells of the immune system leading to the release of pro-inflammatory cytokines<sup>(7, 8)</sup>.

Paracetamol poisoning has complex effects on cellular metabolism, and may cause lactic acidosis into two different scenarios. First, there are numerous reports of severe early lactic acidosis, often with coma, occurring prior to the onset of hepatotoxicity. These occurred in the patients with very large paracetamol overdose (usually more than 40 gm., with peak plasma paracetamol concentrations typically over 800 mg/ml). Many of these patients did not develop liver damage after treatment with N-acetylcysteine<sup>(9-11)</sup>. The second scenario occurs later in the course of paracetamol poisoning. In this group, an elevated arterial lactate concentration has been shown to be a strong predictor of death<sup>(12- 14)</sup>.

This study was aimed to determine the incidence, clinical significance and prediction of early high anion gap (>15 mEq/L) metabolic

acidosis or late lactic acidosis in acetaminophen overdose with the time of N-Acetyl Cystiene (NAC) administration. Besides this, it reports the correlation of late metabolic acidosis and coma in a severe acetaminophen (APAP) overdose with increased mortality.

### Subjects and Methods

This study was designed by the systematic data collection which was carried out by a review of all medical records collected from the files of acetaminophen poisoning cases admitted to Al-Noor hospital, Makkah, KSA during the period of May 1<sup>st</sup> 2009 to May 1<sup>st</sup> 2011.

The cases were selected from inpatient admitted to Al-Noor hospital, Makkah in: pediatric, ICU, and general medicine departments.

According to the laboratory findings, the cases were divided into three groups:

**Group I:** This group included the cases with the toxic ingestion of APAP poisoning and early anion gap acidosis.

**Group II:** This group included the cases with the toxic ingestion of APAP poisoning with late metabolic lactic acidosis.

**Group III:** This group included the cases with the non- toxic ingestion of APAP poisoning.

The ethical approval was obtained from the hospitals where these patients underwent this study.

In this study, the data were collected from the medical records (cases and control) of the patients. The data sheets for personal history, complaint, past and present medical history and laboratory investigations were completed.

#### **Exclusion criteria**

\* The Patients with liver diseases due to any causes other than APAP poisoning

#### **The Laboratory investigation results that had been collected from patients' files were**

1- Serum paracetamol level

- 2- Liver function tests: SGOT ( AST ) , SGPT (ALT)
- 3- Arterial blood gases
- 4- Electrolyte levels
- 5- Serum Lactate

**The laboratory tests have been done by the following methods**

1. Serum Paracetamol level (or other drugs if done): by a high-performance liquid chromatography with electrochemical detection (HPLC-EC) method <sup>(15)</sup>.
2. Liver function tests: SGOT (AST), SGPT (ALT) by automated closed system clinical chemistry analyzer: Dimension RxL Max integrated chemistry system <sup>(16)</sup>.
3. Arterial blood gas: PH, H<sup>+</sup> conc., HCO<sub>3</sub>, PCO<sub>2</sub>, PO<sub>2</sub> by automated analyzer ABL800 FLEX <sup>(17)</sup>.
4. Electrolyte levels (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>) by automated closed system clinical chemistry analyzer: Dimension RxL Max integrated chemistry system <sup>(16)</sup>.
5. Serum Lactate (reference value 0.5 to 1.0 mmol/ L) by automated closed system clinical chemistry analyzer: Dimension RxL Max integrated chemistry system <sup>(17)</sup>.
6. **Calculation of Anion gap = [Na<sup>+</sup>] - [Cl<sup>-</sup>] - [HCO<sub>3</sub><sup>-</sup>]** (normal value 12-15meq/L; high anion gap above 15 meq/L).

**Statistical method <sup>(18)</sup>**

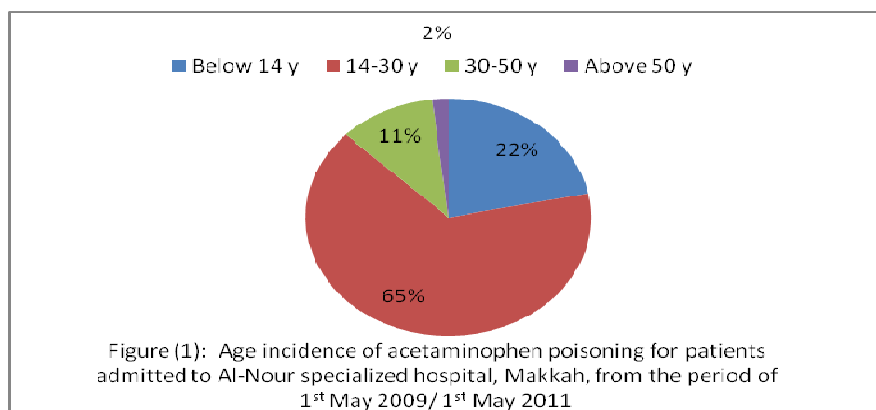
The data are expressed as a percent or mean ± SD. Statistical significance between groups was tested using the students' t-independent test. The statistical evaluations were performed with the Statistical Package for the Social Sciences (SPSS) version 12. Values of P > 0.05 were considered statically non-significant while value P < 0.05 was considered statically significant. The relationship between variables was tested using one way ANOVA test (F test) <sup>(18)</sup>.

**RESULTS**

The fifty five cases were collected from Al-Noor specialized hospital, Makkah region, KSA; fifty five percent was seeking medical advices from the period of (1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011) due to the ingestion of toxic doses of acetaminophen, meanwhile fifteen cases was admitted due to ingestion of a nontoxic dose of acetaminophen.

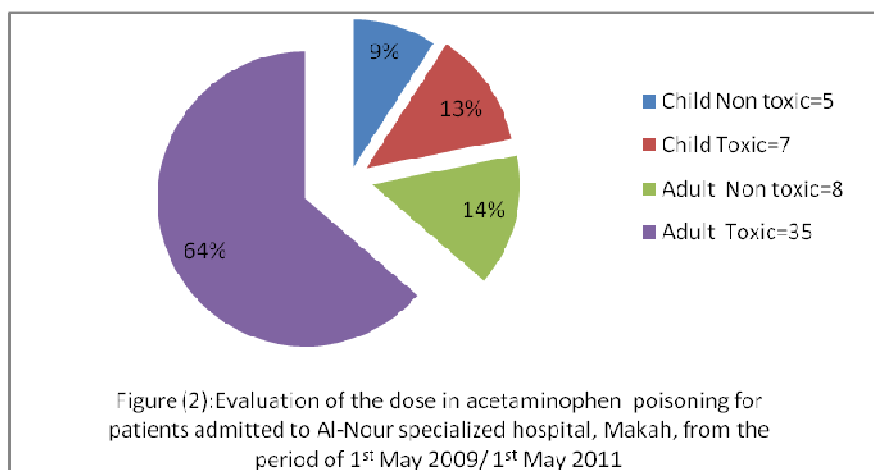
Among the tests, we studied the incidence of APAP poisoning in the fifty five cases and significance of the time of administration of NAC with the development of anion gap or lactic acidosis.

Figure (1) showed that the highest percent (65.45%) was between 14-30 years old, while 21.8% of patients under 14 years, 10.9% between 30-50 years old and just 1.8% of patients aged above 50 years.



The female patients showed the highest percent which was 74.5% (41 cases), while the male was only 25.5 % (14 cases).From the poisoning data sheet as shown in Figure (2), the dose and APAP

level were toxic in 76.36% of cases (12.73% children and 63.64% adult), while 23.64% were ingested the nontoxic dose of APAP (9.10% children and 14.54% adults). Of the total cases, 21.83% (12) cases were children while 78.18% of the cases (43 cases) were adults.



The children's manner of poisoning was accidental while adults were due to suicidal manner. Most of the patients with acetaminophen poisoning had immediately transferred to the hospital (94.54%) while (3.64%) of cases were seeking first aid service from the Saudi Red Crescent and only (1.82%) of cases from the poison control center (PCC) of Jeddah, Table (1).

**Table (1)**

***The medical advice of patients with acetaminophen poisoning admitted to Al-Noor specialized hospital, Makah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

Type of service	Total number=55	%
Immediate	52	94.54%
Red Crescent	2	3.64%
PCC	1	1.82%

In Table (2), most of the patients with acetaminophen poisoning were asymptomatic (74%), then the 2<sup>nd</sup> presenting symptom was vomiting (14.6%) then abdominal pain constituted 10.9% of cases. Most of the cases seek medical advice within 2 hours after APAP poisoning.

**Table (2)**

***The first manifested symptom in patients with acetaminophen poisoning cases admitted to Al-Noor specialized hospital, Makah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

Symptom	Total number=55	%
Vomiting	8	14.6%
Abdominal pain	6	10.9%
Asymptomatic	41	74.5%

Thirty patients with APAP poisoning received medical treatment in the form of gastric lavage (54.5%), on the other hand, 55 patients (100%) received NAC as specific antidote and 50 patients (90.9%) received activated charcoal (Table 3).

**Table (3)**

***The protocol of management of patients with acetaminophen poisoning admitted to Al-Noor specialized hospital, Makah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

Management procedure	Total number=55	%
Gastric lavage	30	54.5%
NAC	55	100%
Charcoal	50	90.9%

Due to variations in poisoning management techniques, the total number of used techniques was more than the calculated number of patients. Although on admission, more than 76% of cases take a toxic dose of APAP as illustrated before in Figure (2), only 18.2% showed an increase in liver transaminases while 81.8% with normal transaminases, and 9.1% showed a late increase in liver transaminases (after 48 hours) but nearly all cases (96.36%) showed within normal transaminases on discharge (Table 4).

**Table (4)**

***The change in Liver enzyme (AST and ALT) in patients with acetaminophen poisoning admitted to Al-Noor specialized hospital, Makah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

	High level		Within normal	
	No.	%	No.	%
On admission	10	18.2	45	81.8
After more than 48 hrs	5	9.10	53	96.36
On discharge	0	0	0	0

Table (5) explained the incidence and time of the acidosis that had been detected in patients with acetaminophen poisoning admitted to Al-Noor specialized hospital. Among 42 patients (76.36%), 33 cases developed acidosis early on admission (high anion gap acidosis), while only 9 cases developed acidosis late (lactic acidosis) but only thirteen patients (23.64%) had no change in blood gases, serum electrolytes, bicarbonate or lactate level.

**Table (5)**

***The Incidence and time of high anion gap in patients with acetaminophen poisoning admitted to Al-Noor specialized hospital, Makah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

	%	No.
Early anion acidosis	60%	33
Late lactic acidosis	16.36%	9
No acidosis developed	23.64%	13

There was a positive significant relation ( $P < 0.05$ ) between (toxic dose of APAP and toxic APAP level) and development of metabolic acidosis as all cases with the toxic ingestion had developed metabolic acidosis as shown in Figure (2) and Table (6).

**Table (6)**

	Non Toxic APAP dose or level (13)	Toxic dose and toxic level of APAP (42)
Development of metabolic acidosis	No cases	42 cases
t test	N.S.	$P < 0.05^*$

There was a significant relation ( $P < 0.05$ ) between the timing of administration of NAC and types of metabolic acidosis. Early administration of NAC in APAP toxic ingestion And toxic APAP level leads to the development of high anion gap acidosis, while late administration of NAC in APAP toxic ingestion and toxic APAP level leads to the later development of lactic acidosis Table (7).

**Table (7)**

***The relation between timing of NAC administration and type of metabolic acidosis***

Number	
33	Early anion acidosis + Early NAC
9	Late lactic acidosis + Late NAC
$P < 0.05$	t test

As shown in Table (8), Group 1 showed significant ( $P < 0.05$ ) correlation of early anion gap acidosis with early antidote administration and low mortality rates in comparison with non -toxic APAP ingestion cases and highly significant ( $P < 0.001$ ) correlation of late lactic acidosis with late antidote administration, coma and high mortality rate in comparison with non -toxic APAP ingestion cases.

**Table (8)**

***The relation between antidote (NAC), metabolic acidosis with prognosis of acetaminophen poisoning cases admitted to Al-Noor specialized hospital, Makkah, from the period of 1<sup>st</sup> May 2009/ 1<sup>st</sup> May 2011***

Groups	Character	No.,	%	Coma / Death	t test
Group 1 *	Early anion acidosis + Early NAC	33	60%	2	$P < 0.05$
Group 2	Late lactic acidosis + Late NAC	9	16.36%	3	$P < 0.001$
Group 3	No acidosis developed	13	23.64%	1	

## DISCUSSION

Paracetamol (acetaminophen) is the most commonly taken drugs in overdose in the UK and is a common cause of overdose morbidity and mortality<sup>(19, 20)</sup>.

Our study aimed to show the incidence, clinical significance and prediction of early or late acidosis with acetaminophen (APAP) overdose.

We collected 70 cases, 15 were considered as control with normal liver functions while 55 cases were seeking medical advice due to ingestion of large dose of APAP. Most of the patients took N-acetyl cysteine within 24 hours of ingestion.

Considering the pattern of age incidence of APAP poisoning we found that there was a high incidence in the group who aged from 14-30 year in comparison to other age groups. On the other hand, William, 2002<sup>(19)</sup>, collected data from 308 patients with acute liver failure who were admitted into seventeen US tertiary care centers over a 41-month period and found that 73% of patients with mean age of 38 years old due to APAP poisoning and showed these results due to excess stressful condition during these periods of life by socioeconomic analysis of them leading to high incidence of suicidal attempt.

Sex incidence of acetaminophen poisoning in our results showed that the females were more affected in comparison to the males. In agreement with our results, William, 2002<sup>(19)</sup> showed that 73% of patients were women who exposed to more stressful condition in comparison to male.

The dose was toxic in 76.36% of cases in which 12.73% were children and 63.64% were adults; Meanwhile 23.64% were ingested non toxic dose of APAP (9.10% children and 14.54% adults). The 78.18% of the cases were in adults and poisoned by suicidal manner while the other cases were in children and poisoned by accident. According to William in 2002<sup>(19)</sup>, the adult cases were more than children with acetaminophen poisoning. In 37% of the patients in his research had taken an acetaminophen overdose with suicidal intent, and 57% of accidental toxicity.

In our study, the cases were mainly asymptomatic in 74.5% of the patients then manifested symptoms were vomiting, and abdominal pain. This could be explained by most of the cases arrived at the hospital within 2 hours after ingestion. Narongchai and Narongchai, 2004<sup>(20)</sup> showed disagreement with our results, as they found that main presenting symptoms were nausea and vomiting in all cases that arrived to poisoning center after 4 hours at least of the ingestion.

The liver transaminases had been measured on admission and regular daily until patients had discharged; most of the patients showed normal enzyme levels on admission (81.9%).

Singer *et al.*, 1995<sup>(21)</sup> agreed with our results as they found in 291 patients with toxic acetaminophen levels who were admitted, only 36 (12%) had increased levels of AST at some point on admission and during hospitalization. They mentioned that the elevations of the AST and ALT with acetaminophen toxicity may not be seen for 36 hours and that; the effects of acetaminophen poisoning may be delayed. It is possible for a patient to have ingested a dangerous amount of acetaminophen within 36 hours of arrival at the emergency department and present with a normal physical exam, no subjective complaints, and normal laboratory values.

In the protocol of treatment in patients with acetaminophen poisoning, 90.9% of the patients receiving activated charcoal as most of the cases seek medical advice within 2 hours after APAP ingestion. Richard *et al.*, 2006<sup>(22)</sup> is in agreement with our results; as they found that activated charcoal (50–60 g) reduced the serum acetaminophen level by 25 % if given within 1 hour after ingestion. In the same study, they found that activated charcoal (1 g/kg) when mixed with soda and given 15 minutes after simulated overdose reduced the acetaminophen absorption by 74%. The

efficacy of activated charcoal decreased when it was administered more than 1 hour after ingestion and no benefit on the 4-hour APAP serum concentration when activated charcoal was given 2–4 hours after simulated overdose.

NAC was given to the entire patient in our study without comparing to the toxic level on The Rumack-Mathew nomogram or measure if the cases took a toxic dose or not (above 140 mg/kg).

In agreement with our results, Richard *et al.*, 2006<sup>(22)</sup> had reported that N-acetyl cysteine (NAC), either in its usual oral or intravenous dosage, is effective at reducing mortality or at reducing the subsequent incidence and severity of liver injury after acetaminophen overdose.

Meanwhile, Adam *et al.*, 2005<sup>(23)</sup> showed disagreement with our results, they determined the need for NAC treatment after an acute ingestion of APAP can only be decided if the level of APAP lies in the toxic level on the Rumack - Mathew nomogram.

In this study, 54.5% of the patients undergo gastric lavage. In agreement with our study, Brook *et al.*, 2006, and Lars *et al.*, 1996<sup>(24, 25)</sup> had described that gastric lavage is done in all cases of APAP poisoning and recommended that gastric lavage is generally the preferred method of decontamination as it able to reduce the absorption of paracetamol and should be considered for untreated patients arriving at a health care facility within four hours after ingestion. Gastric emptying more than four hours after ingestion is not considered helpful.

The relation between antidote (NAC) and high anion gap acidosis in patient with acetaminophen poisoning was detected in 96.36% patients. Patients who don't receive antidote 3.64% had late lactic acidosis. In agreement with our study (study led by Brett Roth, 1999),<sup>(26)</sup> Metabolic acidosis and coma may develop in patients who experience severe hepatic injury after acetaminophen poisoning. The onset of acidosis and coma soon after acetaminophen overdose.

The percentage of the patients that had an early anion gap metabolic acidosis with acetaminophen poisoning in our study was 76.36% which was more comparable to the patients who have late lactic acidosis 23.64%. There was a positive correlation between toxic overdose of APAP and the development of metabolic acidosis with or without elevation of transaminases. Our results were in agreement with Koulouris *et al.*, 1999<sup>(27)</sup> who recoded that severe acetaminophen overdoses could independently cause metabolic acidosis and coma in the absence of laboratory or clinical hepatotoxicity.

The same findings were associated with David *et al.*, 2007<sup>(28)</sup> who suggested that the patients with acute acetaminophen overdose were associated with marked anion gap and metabolic acidosis without hepatic complications (laboratory or clinical). The acidosis fully resolved with *N*-acetylcysteine treatment and supportive care including hydration. They explained these results from the development of type B lactic acidosis with hypoglycemia might have been caused by a deficit in gluconeogenesis secondary to severe hepatic failure and/or a toxic metabolite of acetaminophen.

Also, in agreement with our findings, Zein *et al.*, 2010<sup>(14)</sup> reported early high anion gap metabolic acidosis in 41% of patients on admission and persisted for  $1.5 \pm 0.1$  days. The lactate level increased in proportion to the APAP concentration ( $r = 0.75$ ,  $P < 0.05$ ). Patients with increased anion gap had a higher incidence of confusion and lethargy. Early high anion gap metabolic acidosis were found in the absence of shock or liver failure. Anoop, *et al.*, 2010<sup>(29)</sup>; had the findings agreed with ours and their explanations described that: paracetamol poisoning can result in metabolic acidosis in two different scenarios. First, early in the course of poisoning and before the onset of hepatotoxicity in patients with massive ingestion; metabolic acidosis are usually associated with coma.

Experimental evidence from studies in whole animals, perfused liver slices and cell cultures



had shown that the toxic metabolite of paracetamol, N-acetyl-p-benzo-quinone imine, inhibits electron transfer in the mitochondrial respiratory chain and thus inhibits aerobic respiration. This occurs only at very high concentrations of paracetamol, and precedes cellular injury by several hours. The second scenario in which lactic acidosis can occur is later in the course of paracetamol poisoning as a consequence of established liver failure that result from delayed NAC administration<sup>(11, 29)</sup>.

## CONCLUSIONS

1. Severe acetaminophen overdoses can cause metabolic acidosis in the absence

of rising serum transaminases, so the guidelines on management of APAP poisoning after acetaminophen level is the metabolic acidosis regarding the findings of liver function tests.

2. Early high anion gap metabolic acidosis in patients with APAP predict clinical recovery if rapid administration of NAC occurs.
3. Lactic acidosis may be a marker of severity in paracetamol poisoning
4. Early management of acetaminophen overdose decreases the incidence of metabolic acidosis and subsequently the liver damage.

## REFERENCES

1. The American Dental Association (ADA): acetaminophen overdose and liver damage: *JADA*, 2010; 141(9):1158.
2. O, Grady JG. Paracetamol induced acute liver failure. *Hepatology*, 1997; 26 (suppl.):41-46.
3. Litovitz TL, Klein-Schwartz W, Rodgers GC, *et al.*: Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg. Med*, 2002; 20: 341-352.
4. Kwan D, Bartle WR, and Walker SE: Abnormal serum transaminases following therapeutic doses of acetaminophen in the absence of known risk factors. *Digestive Diseases and Sciences*; 2005; 40 (9):1951–1955.
5. Lee WM: Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology*, 2004; 40 (1): 6–9.
6. Hinson JA., Reid AB., McCullough SS *et al.*: Acetaminophen - induced hepatotoxicity: role of metabolic activation, reactive oxygen/nitrogen species, and mitochondrial permeability transition. *Drug Metab Rev.*, 2004; 36:805-822.
7. Pumford NR, Halmes NC, Martin BM, *et al.*: Covalent binding of acetaminophen to N-10-formyltetrahydrofolate dehydrogenase in mice. *J Pharmacol Exp Ther.*, 1997; 280:501-505.
8. Manov I, Motanis H, Frumin I, *et al.*: Hepatotoxicity of anti-inflammatory and analgesic drugs: ultra structural aspects. *Acta Pharmacol Sin.*; 2008; 27(3):259-272.
9. Roth B, Woo O, and Blanc P.: Early metabolic acidosis and coma after acetaminophen ingestion. *Ann Emerg Med j.*, 1999; 33: 452–456.
10. Noorjah P, Ahmad SR, Karwoski C, *et al.*: Estimates of acetaminophen (paracetamol)-associated overdoses in the united states. *Pharmacoepidemiol Drug Saf.*, 2006; 15: 398–405.
11. Shah AD, Wood DM, Dargan PI.: Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol*, Jan. 2011; 71:20-28.

12. Bernal W, Donaldson N, Wyncoll D, *et al.*: Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet*, 2002; 359: 558–563.
13. Macquillan GC, Seyam MS, Nightingale P, *et al.*: Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure. *Liver Transpl.*, 2005; 11: 1073–1079.
14. Zein JG, Wallace DJ, Kinasewitz G, *et al.*: Early anion gap metabolic acidosis in acetaminophen overdose. *Am J Emerg Med.*, Sep. 2010; 28(7):798-802.
15. Muldrew KL, James LP, Coop L, *et al.*: Determination of acetaminophen-protein adducts in mouse liver and serum and human serum after hepatotoxic doses of acetaminophen using high- performance liquid chromatography with electrochemical detection. *Drug Metab Dispos.*; 2002; 30:446–451.
16. Ghoshal A.K. and Soldin S.J.: Evaluation of the Dade Behring Dimension RxL: integrated chemistry system-pediatric reference ranges. *Clinica Chimica Acta* , 2003; 331, 135–146.
17. Grenache D.G. and Parker C.: Integrated and automatic mixing of whole blood: an evaluation of a novel blood gas analyzer, *Clinica Chimica Acta*, 2007; 375, 153–157.
18. Wayne W .Daniel: Biostatistics. In: A foundation for analysis in the health sciences, 6<sup>th</sup> ed.; John Wiley and Sons press, 1995; 158-162.
19. William Lee, Acetaminophen overdose most common cause of acute liver failure, *Gastroenterology*. 2002; 137: 47-54.
20. Narongchai P, Narongchai S: Paracetamol overdose in suicidal attempt patients. *J Med Assoc Thai.*, 2004 Apr; 87(4):423-426.
21. Singer AJ, Carracio TR, Mofenson HC: The temporal profile of increased transaminase levels in patients with acetaminophen-induced liver dysfunction. *Ann Emerg Med.*; July, 1995; 26:49-53.
22. Richard C. Dart, Andrew R. Erdman, *et al.*: Acetaminophen Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management, *Clin. Tox.* , 2006; 44:1–18,.
23. Adam K. Rowden, Jeffrey Norvell, *et al.*, Updates on Acetaminophen Toxicity, *Med Clin*, 2005, 1148.
24. Brook J, Buckley N, *et al.*: Interventions for paracetamol (acetaminophen) overdose, *Cochrane Database Syst Rev*, 2006:9
25. Lars C. Larsen, Stephen H. Fuller, Management of acetaminophen toxicity. *American Family Physician*; 1996:1-2.
26. Brett Roth, Olga Woo, *et al.*: Early Metabolic Acidosis and Coma after Acetaminophen Ingestion, *American College of Emerg. Phys.*; 1999; 12.
27. Z Koulouris, MG Tierney, and G Jones: Metabolic acidosis and coma following a severe acetaminophen overdose, *The Annals of Pharmacotherapy*. 1999; 33(11): 1191-1194. Harvey Whitney Books Company.
28. David T. Lawrence, DO; Laura K. B *et al.*: 5-Oxoproline–Induced Anion Gap Metabolic Acidosis after an Acute Acetaminophen Overdose. *Turk J Pediatr*. 2007 Jan-Mar; 49 (1):75-76.
29. Anoop D. Shah, David M. Wood1, & Paul I. Dargan1: Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol*. 71(1):20–28.