

## Toxicity Patterns and Outcomes in Acute Acetaminophen Ingestions

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### Abstract

**Objective:** Core idea of this research is to comprehend acute acetaminophen toxicities, towards the determination of N-Acetyl Cysteine, relevant time of onset added by protocol therapy. It also looks into determined outcomes.

**Subjects and methods:** In current research followed retrospective plan of study with a level of eligibility of 307 patients (among whom 200 are males and 107 are females). These patients were from all the age groups and were suffering from acute acetaminophen toxicities as noted within October 2010 to the month of September 2012. These people also have ingestion acetaminophen through intentional/unintentional aspects, and the level of serum acetaminophen under detectable level.

**Results:** Poisoned acetaminophen offers determined percentage as per ER visits of 307 poisoning case within 1884 (that is 16.2%). Just 6.2% of entire acetaminophen toxicities offered possible/probable hepatic toxicities added by NAC as prescribed with nearly noted equal distribution made through intentional as well as unintentional poisoning mode (52.7% or 47.3%).

**Conclusions:** There is complete recovery without any mortality record being featured in current research attributing towards very low chronic alcoholism instances as in relevant case studies.

**Keywords:** Hepatotoxicity; Acetaminophen toxicity; N-Acetyl cysteine

### Introduction

Implication of Acetaminophen on international basis remains counter analgesic agent and is implied accidentally over pediatric exposures added by deliberate sort of self-poisoning aspect [1]. Boutis and Shannon [2] note that acetaminophen toxicity remains as a single drug implied as overdose and resulting in hospital admission. Higher doses of acetaminophen comprise of higher toxicity risk. Moreover, acetaminophen toxicity gets noted through repeated aspect of small doses taken in 24 hrs, exceeding recommended doses. However, overdose of acetaminophen hardly induce sickness among children [3].

Acetaminophen toxicity has three stages – nausea/vomiting, sweating and pallor. It causes in least possible hours from toxic exposure [4]. Next stage has got relevance with occurrence time from 24 to 72 hours in relation with increased risk of hepatic damage; right upper quadrant pain, added by renal impairment with syndrome of multiple organ dysfunction [5]. Third stage is within 4 to 6 days and features hepatic necrosis leading towards hepatic failure added by coagulation defects, followed by hepatic encephalopathy added by failure of multiple organ [6].

Reversibility over acute acetaminophen toxicity remains available in case of early effective intervention attained through N-Acetyl Cysteine (or the NAC). Effective mode of therapeutic protocol led by NAC is documented through diversified literatures as well as tests within efficient mode being toward acute acetaminophen toxicities [7-9].

Basic cause of failure in liver cell is related to cetaminophen toxicity, leading to death in various countries like the UK and the US [10]. Acetaminophen gets noted as single most familiar reason in poisoning state of ingestion among younger children. However, the same remains very rare in terms of children related to the attainment of levels of toxic blood through the syrup of ingesting acetaminophen [11].

Current research concentrates over the provision 1) To understand

acute acetaminophen toxicities status within respective locality. 2) To note frequency in relevance to the acute acetaminophen toxicity type as represented under ER department. 3) To detect mode of hospitalization frequencies, NAC time related to onset as well as protocol therapy. Eventually leading to result of acute paracetmol toxicities as per case studies.

### Subjects and Methods

#### Setting of the research

This research noted three basic hospitals, which are –

- i. Dammam Medical Complex,
- ii. Qatif Central Hospital and
- iii. Dammam Maternal and Child Hospital (DMCH) (community-based secondary care).

All patients from ER department with acute acetaminophen toxicity with acute single/multiple ingestions over acetaminophen as noted in current study. This research follows plan for retrospective study, got 307 patients (among whom 200 are males and 107 are females). Current research we for all determined acetaminophen poisoning under intentional as well as unintentional poisoning, and thus attain wider age frame of 1 to 97 years.

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### Inclusion as well as exclusion criteria

In reference to this retrospective study, there are patients from all age groups and from both sexes. These are people who suffered from the state of acute acetaminophen toxicities, during October 2010 to the month of September 2012 with ingestion acetaminophen through intentional/unintentional approach, that attain level of serum acetaminophen being detectable level. Patient with acetaminophen toxicity, levels of undetectable serum acetaminophen added by level of serum acetaminophen attained accidentally from determined therapeutic dosing made of acetaminophen in relevance to toxicities being excluded from this research.

### Study design

This observational, retrospective, descriptive, cohort design attain assess towards acetaminophen acute toxicity pattern, with management as well as fate in determined cases. The protocol of the study was initiated by the Review Board of Dammam Poison Control Center. Patients are identified by the application of monitoring database of the toxicology clinical through Online Analytical Toxicology Request and Result (or the OTARR). All sorts of electronic mode of reported cases for this study are noted in the time of respective study period.

Records of electronic medical dimension and levels of acetaminophen serum concentration, added by observation time are all reviewed. Pertinent data with laboratory, demographic, and acetaminophen ingested content, degree noted for acetaminophen toxicity per Rumack-Matthew nomogram [12] with respective protocol, time, complications and frequencies from N-Acetyl Cysteine get collected over standardized forms. Moreover, as per former relevant visit of ER, there were circumstantial evidence related to toxicities under detailed report of circumstances meant under acetaminophen toxicities, in the presence of coingestant, amount and form of ingested acetaminophen, poisoning route, lapse of time lapse among poison exposure added by hospital arrival, evaluation score of ED with admission status being abstract.

Acute mode of single ingestions over acetaminophen got ingestion being more than 4 gm in 8 hrs, whereas multiple ingestion acetaminophen toxicities get noted with more than one ingestion over the aspect of acetaminophen within 8 hrs with cumulative dose which appear greater than 4.0 g [13].

Coingestion types remain abstracted from the records of electronic aspects in order to evaluate medication causing hepatic damage. Determined assessment over liver injury has been noted over serum alanine added by aspartate aminotransferase (or the ALT) (AST). The approach is to conform past studies, with severe mode of hepatic injury noted as AST > 1.000 IU/L [14].

### Grouping studied patients

Case studies can remain relevant to the level of serum acetaminophen over Rumack-Matthew nomogram being divided in 3 respective groups, namely - 1. No hepatic toxicity, 2. Possible hepatic toxicity and 3. Probable hepatic toxicity). Moreover, there are descriptive purposes with patient being grouped through presentation type, single/multiple ingestion, aspect of timed serum acetaminophen concentration, with the demand for N-Acetyl Cysteine protocol, under hepatic injured condition caused by acetaminophen toxicity.

### Statistical sort of analysis

Latest SPSS or the statistical package Version 19 is implied to

evaluate data on statistical basis. Data get identified under Mean ± Standard Deviation (or SD). Here there is T-test in contrast relevance to two groups as well as F- Anova being part of contrast multiples with p-values being noted towards statistical entity of an instance like ≤ 0.05.

### Results

The core purpose of table 1 is to illustrate varied demographical features while the case study, which is for the age of about 25% of total study are noted to be under 15 years of age. This is also about 51% of cases that were reported for the adolescent age. In terms of sex, almost 2/3 of case studies are about male with equal percentage of woman (that is 52.7/47.3%) under intentional/non-intentional aspects under acetaminophen poisoning. The research shows rising from respective table 1 to 94% under no hepatic toxicity as possible, whereas 6% are for possible/probable hepatic toxicities.

To a margin of 93% of case studies were for acetaminophen toxicity, represented as single acute ingestion under acetaminophen that is for less than 8 hours, whereas rest percentage represented multiple ingestions over more than 4grams acetaminophen in 24 hours.

As per noted cases (n 19) under N-Acetyl Cysteine (13), there is 68.4% N-Acetyl with less than 10 hrs from toxicity level. Being single course in terms of all, except for one, there is the double NAC parental infusion for progression cessation over hepatotoxic acetaminophen intoxication. Here were two cases that are reported with the information of dermatological reaction being rash and a case suffered from the instance of incomplete recovery with persistent rise in terms of hepatic enzyme.

Parameter	Figure
Age (no 307):	
Range mean ± SD	1-97 (27.6 ± 17.5)
<6 No(%)	50 (16.2)
6-15 No(%)	27 (8.7)
15-25 No(%)	156 (50.8)
>45 No(%)	47 (24.3)
Sex (no 307):	
Male (%)	(200) (65)
Female (%)	(107) (35)
Mode of poisoning (no 307):	
Intentional. No(%)	162 (52.7)
Unintentional. No(%)	155 (47.3)
Degree of toxicity (no 307):	
Paracetamol toxicity degree according to Rumack-Matthew nomogram:	
No Hepatic Toxicity	288 (93.8%)
Possible hepatic toxicity	12 (3.9%)
Probable hepatic toxicity	7 (2.3%)
Pattern of toxicity (no 307):	
Acute single ingestion (within 8 hours) No(%)	284 (92.5%)
Multiple repeated ingestion (>4 gm within 24 hours) No(%)	23 (7.5%)
Time of NAC started treatment from onset of toxicity (no 19):	
(Range/mean ± SD) hr	4-40 / 12.9 ± 9.5
Less than 10 hours	13 (68.4)
More than 10 hours	6 (31.6)
Frequencies of NAC course (no 19):	
Single NAC course	18 (94.7)
Multiple NAC courses	1 (5.3)
Complications of NAC course (no 19):	
Dermatological reaction	2 (10.5)
Anaphylactoid reaction	0 (0.0)
Recovery rate (no 19):	
Complete recovery	18 (94.7)
Incomplete recovery	1 (5.3)

**Table 1:** Features of demographic domain, dosage as well as result in patients with acetaminophen ingestion.

As for table 2 it noted age group difference in various case studies that are unintentional group in a section that is less than intentional group (that is of 22.2 vs. 33.3) year with value of  $p < 0.001$ . Unintentional ingestion for acetaminophen ingestion with higher importance for noted cases rather than intentional intoxication (with  $p 0.04$ ). Table 2 is for N-Acetyl Cysteine therapy under intentional cases over toxicities (between 16 of 19). For others admission status remained higher under unintentional cases rather than intentional acetaminophen ingestion.

Figure 1 is about isolated scattered spot graph noted in terms of acetaminophen blood concentration added by blood sampling time in 1st 24 hrs a sperRumack-Matthew nomogram.

### Discussion

Respective observational retrospective approach gets designed for the identification of incidence, toxicity pattern, status of ER evaluation, indication over N-Acetyl Cysteine medication added by Outcomes figures from acetaminophen ingestion.

As against the pattern of paracetmal acute toxicity under different situation, there are aspects in reference to problem magnitude, degree as well as toxicity pattern, outcome figures under toxic acetaminophen ingestion, without any clear figures about toxicology center for toxicity profile configuration.

For huge cohort study meant for acetaminophen-induced got severe liver injury as analyzed for intentional as well as unintentional acetaminophen toxicity impact over patient.

Application of prospective definition for the pattern of overdose attains equal distribution related to both intentional or unintentional acetaminophen toxicities (with 52.7% or 47.3%). An article about acute acetaminophen toxicity states 75.4% being under the mode of intentional acetaminophen ingestion [15]. Discrepancy noted for increasing unintentional can attribute towards increase in children as represented under accidental acetaminophen toxicity.

For this research 65% male were with increasing percentage over female can lead to higher percentage of patients under acute acetaminophen or compound narcotic ingestion (11%) and all were

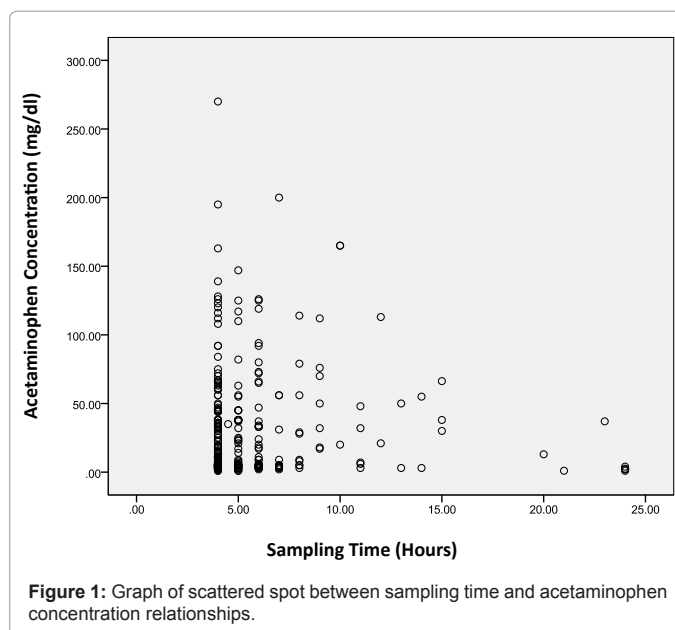


Figure 1: Graph of scattered spot between sampling time and acetaminophen concentration relationships.

male. For age factor being unintentional, mean age remains 33.3 year followed by 22.2 years under unintentional poisoning with difference noted among two poisoning groups. Entire mean age while studying the patients turned up as 27.6 year. As for age sector, there were other two studies with overall high mean in discussing cases through Darren et al. [15] added by Frank et al. [16] with mean age of 34 and 38.1 years respectively. Lowering mean age group can offer attribution towards large unintentional poisoning section in young age group (26.9%).

The strength of this research is its huge numbers of patients, region with single study center and overdose by prospective define criteria. For this study, there is a notable increase in admitted cases under unintentional toxicity pattern, against intentional toxicity route. Cause for this increase can attribute towards large pediatric sector with acetaminophen ingestion history and vague history for all the other vague combined drugs. This admitted patient can be under observation for clarifying degree of toxicity point.

Current research shows 19 (or 6.2%) cases for managing single NAC intravenous infusion protocol added by complete recovery of all the cases except incomplete recovery case (of 0.03%) added by higher function of liver being more than 100% in 2 months.

According to Geeta and Chirage [17] indication percentage related to NAC therapy gets noted as 62% of patient under the group of accidental overdose with 73% patient for suicidal group. Further higher mortality rate of 15% in terms of unintentional exposure cases towards acetaminophen toxicity offers necessary attribution with increased toxicity percentage being mainly caused by late presentation made by patients added by delayed diagnosis, both meant to hinder optimal antidotal treatment under NAC.

There are many studies declaring about higher note of morbidity as well as mortality with acute acetaminophen toxicity between 12% to 41% [18-20]. There is complete recovery without any mortality record being featured surprisingly under current study. This can attribute towards very low incidence related to chronic alcoholism in various case studies with "only two cases 0.06%". Current research shows huge difference in terms for mortality rates among the current research and studies made towards higher percentage of chronic alcoholism.

Variable	Intentional	Unintentional	P
Sex(male/female) no(%)	108/54 (54/50.5)	92/53 (36/49.5)	0.217
Age range/mean $\pm$ SD (years)	15-67 33.3 $\pm$ 17.5	1-97 22.28 $\pm$ 16	0.001
Acetaminophen Concentration(mg/dl)	32.9 $\pm$ 34.4	28.7 $\pm$ 28.7	0.311
Acetaminophen Ingestion Only	85	102	0.041
Compound Narcotic/Acetaminophen Use	18	16	0.436
Mixed Over Dose	45	41	0.233
Received N-Acetyl Cysteine	16	3	0.001
Admission Status (admitted/Not admitted)	24/124	82/77	0.001
Admission Laboratory Parameters			
Platelets ( $\times 10^9 L^{-1}$ )	241 (157-411)	276 (110-391)	0.211
Sodium (mEq/L)	138 (133-141)	135 (131-139)	0.451
AST(IU/L)	33.1 (12-323)	36.3 (6-87)	0.341
ALT(IU/L)	35.9 (6-445)	38.8 (12-132)	0.332
Bilirubin(mg/L)	0.5 (0.1-3.6)	0.56 (0.1-1.7)	0.231
Prothrombin(s)	48 (36-68)	47 (31-63)	0.513
Incomplete recovery	1	0	

P value significant  $\leq 0.05$

Table 2: Admission into clinical as well as laboratory data in patient who are with intentional/unintentional acetaminophen poisoning.

Assumed potentiality of acetaminophen being induced by hepatotoxicity through chronic ethanol ingestion gets discussed illustratively [21-24]. Studies from early 1970s [25] show acetaminophen, considered under therapeutic doses gets metabolized through liver under two pathways. Many drugs (under 80-90%) gets conjugated through glucuronic acid/sulphates, offering nontoxic conjugations excreted by kidney. A minimum number (5%) get metabolized towards reactive electrophilic that is intermediate through cytochrome P-450 system. It renders nontoxic aspect by conjugation made with glutathione to create mercapturic acid in relation with conjugation being excreted by urine. Drug taken excessively that is an augmented amount turns to cytochrome P-450 towards toxic intermediate metabolite with highly reactive instance [25,26]. It can overwhelm protective mechanism over glutathione conjugation added by covalent binding towards hepatocyte proteins that leads towards hepatocellular necrosis [27].

Very least acetaminophen doses even turn up therapeutic with potential aspect causing liver damage, in case the same is connected to respective circumstances, enhancing activity of P-450 system with increased production made over toxic metabolite or the instance to interfere with protective mechanism through depleting aspect of available glutathione. Ethanol has potentiate damage caused by these reasons [21-24].

## Summary and Conclusion

According to present research, acetaminophen poisoning is subject to represent important percentage of ER visits being noted as 307 in 1884 (that is 16.2%) visits of poisoning case. Just 6.2% of entire acetaminophen toxicities offer determined hepatic toxicities added by NAC as prescribed for the same. Mortality rates gets noted as 0% with complete recovery rate in all cases, (except one under incomplete recovery) by persistent impaired hepatic function. This gets increased aspect being more than 100 IU/L in 2 months. Rate of complete recovery without mortality in terms of reported acetaminophen toxicity can attribute towards rarity in relation with chronic alcoholism under recorded cases.

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