# Late Diagnosis of Paracetamol Poisoning is Always Lethal in Young Adult

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# ABSTRACT

Acetaminophen has a remarkable safety profile when prescribed in proper therapeutic doses, but hepatotoxicity can occur when misused or after an overdose. The principal toxic metabolite of acetaminophen is N-acetyl-p-benzoquinone imine (NAPQI). Toxicity should be considered in all suspicious cases because of the ubiquitous and initially asymptomatic nature of acetaminophen intoxication. A case of 29-year male soldier is discussed, who presented with pain in abdomen, vomiting and jaundice of sudden onset. The diagnosis of ischemic liver damage was made at initial presentation. Raised liver function tests and elevated prothrombin time were the first indication to this condition, which were proven by detection of acetaminophen in blood and urine by liquid chromatography-mass spectrometry. Further supportive evidence of hepatic necrosis was provided by an ultrasound abdomen, giving the final diagnosis of acetaminophen poisoning causing drug-induced liver injury.

**Key Words:** Acetaminophen poisoning, Drug-induced liver injury, Fulminant hepatic failure, N-acetylcysteine, N-acetyl-p-benzoquinone imine (NAPQI).

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# INTRODUCTION

According to USA documented data, acetaminophen or Nacetyl-para-aminophenol (APAP), commonly sold as paracetamol, is the most widely used analgesic and antipyretic. The dose of up to 4000 mg per 24 hours of acetaminophen is safe as advertised by the US Food & Drug Administration (FDA) and does not produce toxic effects. If the dose exceeds above 150 mg/kg as a single dose, toxic effects are produced resulting in liver failure. About 90 percent of the APAP is channeled into phase II metabolic pathway and converted to glucouronidated and sulfated metabolites, which are eliminated from the body in the urine.<sup>1</sup> Almost 10 percent of the APAP is shunted by cytochrome (CYP) 2E1 to phase I oxidation, resulting in formation of a highly reactive toxic metabolite, known as, N-acetylpara-benzo-guinone imine (NAPQI).<sup>2</sup> A very small amount, *i.e.*, almost two percent of APAP is excreted unchanged in the urine. Hepatotoxicity induced by acetaminophen overdose occurs through production of the harmful NAPQI metabolite. When present in excessive quantities, it results in depletion of glutathione, oxidative stress and mitochondrial dysfunction leading to depletion in adenosine triphosphate (ATP) stores.

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Correct initial diagnosis of paracetamol overdose is critical. Timely identification and early therapy may prevent significant morbidity and mortality.

Four established sequential stages of paracetamol-induced hepatotoxicity should be considered upon presentation to clinic (Table I).

Stage	Time post ingestion	Description		
Recovery phase	First 24 hours	Nonspecific symptoms like anorexia, nausea, vomiting.		
	24 - 72 hours	Right upper quadrant abdominal pain (common). In severe poisoning, AST, ALT bilirubin and PT (usually reported as the INR) elevated. Persistant Vomiting with symptoms of liver failure.		
	72 – 96 hours	Peaking of serum ALT, AST, bilirubin, and INR.		
	After 96 hours	Resolution of hepatotoxicity or progression to multiple organ failure.		

Table I: Stages of paracetamol-induced hepatotoxicity.

Rumack-Matthew nomogram is a widely acceptable tool used in the management of acetaminophen overdose.<sup>3</sup> It is applicable only in the event of single acute ingestion or if the acuity of ingestion is known to be within 24 hours. Acetaminophen-induced liver injury is known to raise serum aminotransferases above 10,000 IU/L.<sup>4</sup> New biomarkers available are acetaminophen / cysteine protein adducts which indicate exposure to acetaminophen.<sup>5</sup>

Parameters	Day 1 of referral	Day 2	Day 3	Day 4
1.Total bilirubin µmol/l (0-17)	414	606	686	938
2.Serum ALT U/l (upto 42)	7046	1843	2591	279
3. Serum ALP	148	152	180	113
4. serum AST U/l ( <sup>°</sup> 37 )	Not done	5035	2361	Not done
5. Prothrombin time (0-14 sec)	16	18	20	20
6. Hemoglobin level g/dL	10.5	Not done	9.8	10.5
7.Serum Gamma GT U/I (upto 50 U/I)	72	Not done	Not done	53
8.Total leucocyte count (4-10 * 10 <sup>9</sup> /L)	17.4	Not done	37.9	63.2
9. serum urea mmol/l (2.1- 4.7)	Within normal reference limits	4.2	9.9	9.2
10. serum creatinine mmol/l (80-115)	Within normal reference limits	109	398	304
	Hepatitis B (HBsAg): Negative	serum LDH: 9928	PTTK: 54 (0-32 sec)	PTTK: 56 (0-32 sec)
	Acetaminophen level (blood): 9874 ng/ml	Acetaminophen level (blood): 6358 ng/ml	Acetaminophen level (blood): 1544 ng/ml	Acetaminophen level (blood): Undetectable
11. Other	Hepatitis C (Anti HCV): Negative	Acetaminophen level (urine): Positive	Serum K: 5.6 mmol/l	Nasobronchial lavage for C/S: Negative
	Serum ferritin: (24-336 ng/ml): 63433	Acetaminophen level (gastric lavage): Negative	Serum CK: 3135 (25-195 U/l)	lgG Antibody to mycoplasma pneumoniae: Negative
	CMV-DNA PCR (Quant): Negative	Liver kidney microsomal antibodies: Negative	Serum CK-MB: 187 (<25 U/l or <6% of CK)	lgM Antibody to mycoplasma pneumoniae: Negative
		Alpha fetoprotein: 4.7 ng/ml (<8.5)	Fluid for C/S: negative	

Treatment includes oral or intravenous N-acetylcysteine, a glutathione precursor that inactivates and converts NAPQI to harmless metabolites.<sup>6,7</sup> Overall, timely identification and prompt treatment of acetaminophen overdose is critical because it can lead to significant morbidity and mortality, if untreated.

# **CASE REPORT**

A 29-year male soldier was referred from Central Military Hospital, Mardan, on 30<sup>th</sup> March 2019 after 5 days of hospital stay with a provisional diagnosis of ischemic liver damage. He was immediately admitted in Pak Emirates Military Hospital (PEMH), Rawalpindi, and transferred to Armed Forces Liver Transplant Unit.

Patient was in the usual state of health six days back when he suddenly developed pain in abdomen localized to the right upper quadrant along with recurrent vomiting and diaphoresis. Later on, he developed jaundice. Despite continued deterioration, no suspicion of paracetamol poisoning was made. A detailed general physical examination was carried out, which revealed bilateral scleral icterus and diffuse jaundice. Upon abdominal examination, marked tenderness over right upper quadrant was observed, while no abnormality was detected on his cardiopulmonary examistay at PEMH are shown above in the Table II.

nation. His significant laboratory findings during his hospital





By day 2 of referral, patient went into acute fulminant hepatitis but no specific cause was established. The managing team sent the blood to Armed Forces Institute of Pathology (AFIP), Rawalpindi, for paracetamol levels. Acetaminophen (blood) levels were found to be 6358 ng/ml. The patient deteriorated with rapid rise in serum total bilirubin.



Figure: 2 Liquid chromatography-mass spectrometry chromatogram of this patient, showing significant peak of acetaminophen when analysed.

By the third day of referral, despite intensive care and appropriate medication, the patient progressed to multisystem organ failure with poor prognosis and developed ascites with neurological symptoms. Conservative treatment was recommended. On day four of referral, the liver transplant team marked him as the poor candidate for liver transplant due to poor prognosis and multiple organ system failure, so conservative treatment was continued. Registrar toxicology department retrieved the patient's past sample taken at the admission from the PEMH Hospital, Rawalpindi and performed acetaminophen level (blood), which was found to be 9874 ng/ml, *i.e.*, greater than the levels observed on the 2nd day of referral.

Based on above mentioned findings, this case was labelled as drug-induced liver injury progressing to multi-system organ failure. Poor prognosis, complications and the course of illness of the disease were counselled to the family. Maximal pressor support was given and the patient was managed on the ventilator. Despite continued efforts of the medical team, he became unresponsive, continued to decline and expired.

## DISCUSSION

Acetaminophen is the commonest over the counter (OTC) analgesic readily available in the market. According to the US data, it comprises 50% of cases of drug-induced liver injury. The patient discussed above is the classic case of acute acetaminophen poisoning, who presented with severe abdominal pain in the upper right quadrant, coagulopathy, diffuse jaundice and hepatomegaly along with biochemical evidence of significantly raised serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin levels and associated deranged renal function tests leading to multi-system organ failure. As the time of ingestion was not known in this case, the Rumack-Matthew nomogram for prediction of hepatic injury could not be applied. Based on the above mentioned clinical picture, biochemical findings and radiological evidence of hepatomegaly along with peri-portal and gall bladder wall edema, a diagnosis of drug-induced liver injury due to acetaminophen overdose was made.

Acetaminophen-protein adducts using high-performance liquid chromatography (HPLC) is a latest test available for assessing APAP-induced hepatotoxicity.<sup>8</sup> Several other clinically important serum markers indicating mitochondrial damage including glutamate dehydrogenase (GDH), nuclear DNA (nDNA) and mtDNA are increasingly being used.<sup>9</sup> Early molecular biomarker, miRNA-122 is also available for assessing hepatic injury. It notably increases even before the rise of serum ALT levels. These pertinent laboratory tests support collection of clinical findings for better prediction of patient's prognosis, morbidity and mortality.<sup>10</sup> It will broaden the horizon and will clear the queries regarding treatment protocol and decision making.

A multidisciplinary approach is vital in dealing with these cases. The treating panel should also include a psychiatrist as well. Detailed psychiatric assessment should be made mandatory, especially in patients who have intentionally overdosed on acetaminophen. Awareness programmes should be arranged to educate people to avoid its misuse. Advance therapeutic and clinical researches should be carried out for better understanding of molecular and sub-molecular pathways.<sup>11</sup> It will help combat hepatic damage at very early stage. Molecular advancements in the field of health and medicine will prove as a game-changer to tackle this devastating yet curable event.

### **CONFLICT OF INTEREST:**

The authors declared that they had no conflict of interests.

### **PATIENT'S CONSENT:**

Consent could not be taken due to critical condition and then the death of the patient.

## **AUTHORS' CONTRIBUTION:**

All authors contributed to the study design, interpretation,

drafting and preparation of the manuscript and have read and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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