Case Report

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Paracetamol Overdosing With 6500 mg Single Dose: Case Report

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SUMMARY

Introduction: Paracetamol is available as a fixed dose combination with many non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen, Diclofenac, Mefenamic acid, Aceclofenac etc. On the other hand, it is also considered as the most common cause of overdosing and poisoning. Paracetamol can be purchased both by prescription or as an OTC medicine.

Case report: This paper represents a case of a male, age 27, vegetarian, who does regular exercise, alcoholic, who self-overdosed with 6500 mg (~10 tablets of 650 mg each) of Paracetamol with suicidal intention. An attempt has been made to discuss the effects of Paracetamol on liver, kidney and other organs function through hematology, biochemistry, urine investigations done within 24 hours and day 7 after overdosing. Results of additional investigations such as liver function tests done on day 4 and day 5, X-ray chest, ultrasound scan of the abdomen and ECG done on day 1 were also included for discussion. Liver parameters were checked for presence of Drug Induced Liver Injury (DILI) using an algorithm published by Pineda S L et al.

Conclusion: Results of this case analysis suggested the presence of mild DILI with a single dose of 6500 mg Paracetamol. We recommend further studies using algorithm of Pineda S L et al to assess the minimum doses that are expected to cause clinically significant DILI and recommend policies to drug regulators of the country to restrict the maximum number of doses that can be sold to the general public on OTC basis.

Keywords: Paracetamol Overdosing, Drug Induced Liver Injury, OTC Medication Restriction

INTRODUCTION

Paracetamol (Acetaminophen) was discovered in 1878 by Haromon Northrop Morse. It has been on market for more than 140 years. Still it is the most frequently prescribed drug. It is also the most frequently purchased over-the-counter (OTC) medication. During Covid-19 pandemic, Paracetamol is consumed by almost every patient that was affected by SARs COV-2 virus. It is considered as one of the safest and most affordable antipyretic agent [1,2,3].

Paracetamol is available as a fixed dose combination with many non-steroidsal anti-inflammatory drugs (NSAIDs) such as Ibuprofen, Diclofenac, Mefenamic acid, Aceclofenac etc. On the other hand, it is also considered as the most common cause of overdosing and poisoning. Paracetamol can be purchased both by prescription or as an OTC

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medicine. Various formulations are available including syrup, tablets, suppository and injections. In pediatric age group, overdosing is common and among adult patients, self-poisoning is common [1,2]. Reports from western countries (UK, Denmark etc.) suggested that incidence of overdosing increased from 14.3% to 47.8% between 1976 to 1993 [1].

Individual case studies (ICS) represent a relevant, timely, and important study design in advancing medical scientific knowledge as every case is different and adds to our understanding of aetiology, pathogenesis, natural history, and treatment of the disease. They also act as important training material for potential junior investigators [4]. The objective of this article is to present a case of overdosing with 6500 mg Paracetamol, and its management. Also an attempt will be made to present briefly a review of literature regarding Paracetamol overdosing.

CASE REPORT

A male, age 27, vegetarian, does regular exercise, had confrontation with parents. His parents scolded him for business losses and he decided to commit suicide. He had a history of alcohol consumption since 1 month, and had alcohol equivalent to 90-180 ml on the day of Paracetamol self-overdosing. He purchased 10 tablets of Paracetamol 650 mg from a local pharmacy and consumed the same at around 18.00 hr. Once he started feeling dizziness, he informed his parents about this.

His parents shifted him to nearby community health centre. Immediately the doctors conducted stomach wash and referred him to a higher centre for further management. After this, patient reported to our hospital with one episode of vomiting at around 10:00 pm (approximately 4 hours after overdosing). The patient does not have a history of diabetes, hypertension, tuberculosis etc. No other significant medical history regarding on-going disease or treatment was found.

On general physical examination patient was found to have normal physique, moderately nourished, with no other abnormality. Body temperature 98.6 F (37°C), pulse 96 bpm, respiratory rate 20 per min, blood pressure 146/54 mmHg, random blood glucose level 123 mg/dl. Systemic examination did not reveal any abnormality.

According to Glasgow coma scale patient obeys commands, localizes pain, eye opening was spontaneous, and verbal commands elicited relevant talks, but disoriented by place.

Integumentary system assessment revealed total score of 15/23. Sensory perception ¾, moisture ¾, mobility ¾, activity ¾, nutrition ¾, friction and shear 3/3, pain assessment suggested mild discomfort (FLACC score - Facial expression; Leg movement; Activity; Cry; and Consolability) [5]. Fall risk status found to be medium.

Patient was monitored for Blood pressure, Pulse, Respiratory rate, SPO_2, Temperature. All the values were within normal range. Systolic BP varied from 110-140 mg of Hg, Diastolic BP from 60-90 mm of Hg. Pulse rate was between 72-98 beats per minute. Respiratory rate was between 18-22/minute. SPO_2 was maintained between 96-99%. Blood examination was done for haematology, biochemistry parameters within 24 hours and on day 7 after poisoning. Details regarding the test results are given in Table 1. Liver function tests were also monitored within 24 hours, day 4, day 5, day 7 after overdosing. Details of results are given in Table 2.

Treatment of the patient

The patient was treated with supportive and definitive treatment measures. Supportive treatment included continuous monitoring of vital parameters, intravenous fluid infusion to ensure sufficient hydration, injection of multivitamins including vitamin B12 (Inj Optineuron, manufactured by Lupin Ltd) once per day, injection of Pantoprazole (Inj Pan manufactured by Alkem Laboratories Ltd) 40 mg IV twice daily (BD), antacid fixed dose combination (FDC) syrup containing Oxethazaine (10 mg/5ml), Aluminium Hydroxide (0.291 gm/5ml), and Milk of Magnesia (98mg/5ml) (Syrup Mucaine Gel manufactured by Pfizer Ltd) as and when required (SOS) and Injection Ondansetron (Inj Emeset manufactured by Cipla Ltd) 4 mg IV SOS.

Definitive treatment included, 50 gram Charcoal (Rcol Powder manufactured by West-Coast Pharmaceutical Works Ltd), Glutathione Tablet 500 mg (Tab Maxiliv manufactured by Zuventus Healthcare Ltd) BD, FDC of hepatoprotective formulation containing Lecithin, Silymarin, Glutathione, Zinc, Aminoacids, Vitamins (Tab Heptagon manufactured

Table 1. Laboratory investigations results

Name of test	Normal Reference range	Within 24 hours	day 7	Comments
S. Sodium	135-145 mmol/dl	142	144	
S. Potasium	3.5-5.1 mmol/dl	3.9	3.8	
S.Chloride	97-111 mmol/dl	112	112	
S.Urea	17-43 mg/dl	32	17	
S. Creatinine	0.7-1.18 mg/dl	1.01	0.93	
Random Glucose	70-140 mg/dl	123	113	
Hb%	13-17 g/dl	15.2	16.1	
RBC	4.5-5.55 mil/cumm	4.71	4.57	1. S. Urea level within 24 hours of poisoning was double than that recorded at 7th day.
PCV	40-55%	41.6	43.3	
MCV	83-103 fl	88.2	94.8	
MCH	27-32 pg	32.4	35.2	2. All the other parameters were within normal limit.
MCHC	31.5-34.5 gm/dl	36.7	37.2	
RDW	11.6-14.0%	19.4	12.7	
Total Count	4000-10000 cells/cmm	5070	7750	
Neutrophils	40-80%	71	62	
Lymphocytes	20-40%	25	34	
Monocytes	2-10%	03	03	
Eosinophils	1-6%	01	01	
Basophils	0-1%	00	00	
Platelets	1.5-4.41 L/cmm	2.54	3.07	
ECG recorded within 24 hours reported to have normal parameters with sinoatrial rhythm				
SARSCOV2 testing was negative				

by Sun Pharmaceutical Industries Ltd). Injection N-Acetyl Cysteine (NAC) (Mucomix 1 g Injection manufactured by Samarth Life Sciences Pvt Ltd) was initiated on day 3 (within 72 hours after overdosing). Total dose of NAC was divided and given as follows: 9 g in 200 ml normal saline over 1 hour; 3 g in 200 ml normal saline over next 4 hours; and 6 g in 200 ml normal saline over next 16 hours. In addition psychological evaluation and psychotherapy done by a psychiatrist.

DISCUSSION

Paracetamol is rapidly absorbed in the intestine. Upto 50-60% of it is excreted as inactive conjugate of glucuronidation and sulfation. But 5-15% is metabolized by Cytochrome P450 isoforms (such as CYP2E1, CYPE2A6), and converted into reactive metabolite N-acetyl-para-benzo-quinone imine (NAPQI) which is a hepatotoxic chemical. Up to 2% is excreted unchanged [6]. As per several epidemiological studies, the therapeutic dose of 4 g per day in adults and 75 mg/kg in children is considered to be safe. Up to 2.6% of adults were reported with acute liver injury with this dose [7]. Even doses of 125 and 150 mg/kg are believed to cause hepatotoxicity in adults. Dose of 10 to 15 g per day in adults and 150 mg/kg in children is considered as the threshold dose for hepatotoxicity [8]. When Paracetamol is given in therapeutic doses, hepatic Glutathione conjugates NAPQI quickly, before elimination through urine. Toxic doses of Paracetamol lead to Glutathione depletion resulting in raise of NAPQI levels to toxic concentrations. This in turn leads to mitochondrial dysfunction leading to superoxide and nitric oxide reaction and release of free radicals and oxidative injuries. Hepatocytes DNA fragmentation, and cessation of ATP production leads to increased cell permeability, cellular swelling, vacuolization, karyolysis and the loss of cellular elements such as Alanine aminotransferase (ALT). This raise in ALT indicates hepatocytes necrosis [6]. According to reports, increase in hepatic enzymes (AST, ALT, Lactate dehydrogenase and its isoenzymes may increase up to 500-fold within 7-20 days after overdosing/poisoning [9].

Table 2. Liver Function tests results

Name of test	Normal Reference range	Within 24 hours	day 4	day 5	day 7	Comments
Total Bilirubin	0.3-1.1 mg/dl	0.9	2.61	0.80	0.55	Raised on day 4
Direct	<0.2	0.3	0.83	0.26	0.14	Returned to normal on day 7
Indirect	0.0-0.3	0.6	1.78	0.54	0.41	Raised throughout hospital stay
Total Protein	6.4-8.3 g/dl	6.5	6.1	5.7	7.0	Reduced on day 4 and 5
Albumin	3.5-5.2 g/dl	3.2	3.0	2.9	4.2	Reduced till day 5
Globulin	2-3.5 g/dl	3.3	3.10	2.8	2.8	Within normal limit
A/G ratio	1-2.1	0.97	0.97	1.04	1.5	Reduced till day 4
AST	<50 IU/L	126	104	51	144	Raised throughout hospital stay
ALT	<50 IU/L	50	53	37	74	Variable response
AST/ALT	<1	2.52	1.96	1.38	1.95	Raised throughout hospital stay
ALP	53-128 IU/L	126	111	80	64	Declining trend seen from the day of admission
GGT	<55 IU/L	391	388	304	707	Raised throughout hospital stay
Urine examination done on day 2 demontrated presence of Calcium oxalate crystals. Other parameters within normal limit						
Ultrasound examination done within 24 hours reported to have mildly altered echo texture of liver suggestive of Hepatitis. Internal echoes within urinary bladder seen; to be correlated with urine examination. Other parameters considered within normal limit.						

Critical analysis of liver functions tests indicated the marginal raise in total bilirubin (both direct and indirect), AST, ALT, AST/ALT ratio, and GGT and reduction in total proteins and albumin levels. Ultrasound (USG) examination revealed mildly altered echo texture of liver suggestive of Hepatitis. All these results were observed before day 7 after overdosing. These results are in line with the reports of Thomas et al [9]. AST levels rose, but slightly less than 3-fold the upper reference range. Results of liver function tests did not show chemically induced liver injury. Considering results of other investigations (USG) and Pineda SL et al., algorithm this is regarded as a case of mild DILI (as per, ALT or AST ≥3.0 X ULN with the appearance of fatigue, nausea, vomiting, upper abdominal pain, fever, rash, and/or eosinophilia (>5.0%) criteria as published by Pineda SL et al.) [10].

Some patients (upto 2% of patients) may have renal failure and report with signs/symptoms like back pain and renal tenderness with hematuria and proteinuria [9]. In this case no signs of renal injury were identified. Hematological parameters, serum electrolytes and ECG were within normal limit.

In the present case, patient had taken alcohol in addition to paracetamol overdosing at the time of reporting to our hospital. He was conscious but disoriented by place. As per literature, only plasma concentration over 1000 mg/L may reduce the level of consciousness [9].

CONCLUSION

Fulminant liver injury is common with paracetamol overdosing/poisoning. Patient in our report was identified as a case of mild drug induced liver injury (DILI) based on Pineda SL et al algorithm. But it may not be a chemical alone induced liver injury. In alcoholic patients dose of paracetamol as low as 4 g can lead to toxicity. This patient was habituated to alcohol abuse, and consumed alcohol along with 6500 mg (~10 tablets) of Paracetamol, which resulted in mild DILI. It is hence suggested to have regulations in place to control the bulk purchase of Paracetamol on OTC basis by the general public. To come up with such regulations, additional evidences are required to substantiate the claims and therefore we recommend to conduct additional studies using Pineda SL et. al., algorithm along with other clinical features to assess the minimum

dose that can cause DILI. Based on the results, recommendations may be submitted to Drug Controllers General of India (DCGI) to restrict the maximum number of tablets that can be sold to the general public without prescription.

LIMITATIONS

In our case report hepatic functions were monitored only till day 7 after overdosing; hematology and renal functions tests were done only two times i.e., within 24 hours and day 7 after overdosing; and plasma levels of Paracetamol was not estimated. Special features of this study are, patient had alcohol in addition to paracetamol overdosing and NAC therapy was initiated within 3 days after overdosing.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Predoziranje paracetamolom sa 6500 mg u jednoj dozi: prikaz slučaja

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KRATAK SADRŽAJ

Uvod: Paracetamol je dostupan kao kombinacija fiksne doze sa mnogim nesteroidnim antiinflamatornim lekovima (NSAID) kao što su ibuprofen, diklofenak, mefenaminska kiselina, aceklofenak itd. S druge strane, smatra se i najčešćim uzrokom predoziranja i trovanja. Paracetamol se može kupiti i narecept ili kao lek bez recepta.
Prikaz slučaja: Ovaj rad predstavlja slučaj muškarca starog 27 godina, vegetarijanca, koji redovno vežba, alkoholičara, koji se sam predozirao sa 6500 mg (~10 tableta od 650 mg svaka) paracetamola sa samoubilačkom namerom. Ovo je pokušaj da se diskutuje o dejstvima paracetamola na funkciju jetre, bubrega i drugih organa putem analiza krvne slike, biohemije, ispitivanja urina u roku od 24 sata i 7. dana nakon predoziranja. Rezultati dodatnih ispitivanja kao što su testovi funkcije jetre rađeni 4. i 5. dana, rendgenski snimak grudnog koša, ultrazvučni pregled abdomena i EKG urađen 1. dana takođe su uključeni u diskusiju. Parametri jetre su provereni na prisustvo oštećenja jetre izazvane lekovima (DILI) korišćenjem algoritma koji su objavili Pineda S. L. i saradnici.
Zaključak: Rezultati analize ovog slučaja ukazuju na prisustvo blage DILI sa jednom dozom od 6500 mg paracetamola. Preporučujemo dalje studije uz korišenje algoritma Pineda S. L. i sar. za procenu minimalnih doza za koje se očekuje da će izazvati klinički značajan DILI i preporučujemo politiku regulatorima telima za lekove u zemlji da ograniče maksimalan broj doza koje se mogu prodati široj javnosti bez recepta.

Ključne reči: predoziranje paracetamolom, oštećenje jetre izazvana lekovima, restrikcija lekova u slobodnoj prodaji

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