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Paracetamol Toxicity in a 5-Year-Old Child: A Case Report

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Abstract

Introduction: Paracetamol is the most common analgesic and antipyretic that is used in the hospital setting and as over the counter medication and is commonly preferred in pediatric patients. In pediatric population, the dosage error accounts for most cases of acetaminophen toxicity. Paracetamol poisoning may be as a single acute ingestion or as a result of the repeated use. Symptoms vary depending on the stage the patient is in. Serum ALT is routinely used in the diagnosis of hepatic injury following Paracetamol overdose. N-acetylcysteine (NAC) is used as an antidote for Paracetamol toxicity. The antidote helps in replenishing liver glutathione level, thereby increasing the safe detoxification of N-acetyl-p-benzoquinone imine, NAPQI. **Case Presentation**: We present the case of a five years old male child known to have Spastic Quadriplegic Cerebral Palsy with Epilepsy on regular medication. He was admitted in the hospital with complains of productive cough associated with difficulty in breathing and fevers. Clinically on admission he was ill looking, febrile T- 38.7˚C, and pale, with lower limbs non pitting edema. His weight was 13.7 kgs, length of 105cm and his Body mass Index (BMI) was 12.4 kg/m^2. On his respiratory system examination he had nasal flaring, lower chest wall indrawing and bilateral basal crepitation more on the right lung. The diagnosis was Spastic Quadriplegic Cerebral Palsy with Aspiration Pneumonia. He was started on IV Cefriaxone 350 mg 12 hourly, IV Metronidazole 130 mg 8 hourly and Paracetamol suppository 250 mg 6 hourly. On the third day in the ward, he started developing jaundice and he had severe vomiting more than 5 episodes per day. He was also found to have elevated liver functions (ALT 1218 U/l, AST 197.2 U/l). Acute Liver Failure was suspected due to Paracetamol toxicity and we initiated N-acetyl-cysteine (NAC) 1900 mg orally through the nasogastric tube STAT, then continued with 1000 mg orally every 4 hours 31 doses along with multivitamin 2 mls orally once a day, high carbohydrate diet. On day 9, the liver functions had normalized, there was tinge of jaundice with no edema and the

patient was discharged to come for Paediatric follow-up clinic. **Conclusion:** Paracetamol is a commonly used drug, especially among Paediatric patients with potential for overdose. Paracetamol poisoning can lead to liver failure with possible fatal development in children. Reversal of Paracetamol toxicity is dependent on early identification with early initiation of appropriate medication. We advocate for increased awareness among clinicians on the appropriate dosage of Paracetamol specific to the type and nutritional status of the individual.

Subject Areas

Pediatrics

Keywords

Paracetamol Toxicity, Arusha, N-Acetylcyteine Cysteine (NAC)

1. Introduction

Paracetamol is the most common analgesic and antipyretic that is used in the hospital setting and as over the counter medication and is commonly preferred in pediatric patients [1]. In pediatric population, the dosage error accounts for most cases of acetaminophen toxicity [2]. Paracetamol poisoning may be due to only one acute ingestion or as a result of repeated use [3]. The minimum dose of acetaminophen that can cause toxic effects in children for a single acute ingestion is 150 mg/kg. However, it has been suggested that in children between the ages of 1 - 6 years who are healthy, this value should be increased to 200 mg/kg due to less susceptibility to hepatotoxicity from acute acetaminophen toxicity in this age group [4]. The recommended dose for oral or rectal Paracetamol in symptomatic fever (temperature > 38.5˚C) is 15 mg/kg every 6 hrs (< 60 mg/kg/day) whereas the recommendation for analgesia is 15 mg/kg every 4 - 6 hourly, up to a maximum of 60 - 90 mg/kg/day for oral dose and the rectal dose being 20 mg/kg/dose every 6 hourly, up to a maximum of 90 mg/kg/day [5].

When a therapeutic dose is administered, Paracetamol is metabolized primarily (about 90%) through "first pass" metabolism in the liver via glucuronidation and sulfation [6]. In addition, a small fraction (5% - 15%) of Paracetamol is metabolized by CYP450 enzymes (mostly the CYP1A2, CYP2E1, CYP3A4, and CYP2A6 isoforms). This reaction results in the production of N-acetyl-p-benzoquinoneimine (NAPQI), a reactive intermediate of very high toxicity [6] [7]. Glutathione reduces NAPQI to nontoxic mercaptate and cysteine compounds, which are then safely excreted by the kidneys or bile [8]. When there is an overdose, the primary means of Paracetamol metabolism (phase II conjugation) may become saturated, and more of the Paracetamol metabolism is diverted into the CYP450 route, resulting in more accumulation of NAPQI [6] [9]. The glucuronidation capacity of the liver depends on the stores of carbohydrate such that in malnour-

ished individuals, more Paracetamol will be converted to NAPQI. Glutathione stores are also dependent on nutritional status, as malnutrition leads to its depletion [10].

Four stages of Paracetamol intoxication exist. At stage one, symptoms occur shortly after poisoning and are unspecific [11]. They often include nausea, vomiting and malaise. After one to two days the initial clinical findings diminish, but abdominal pain may occur. In this stage abnormal laboratory values are often observed, including elevated liver enzymes, increased bilirubin and prolonged Prothrombin time [11]. Stage three consists of the reappearance of initial unspecific symptoms. In addition, liver function parameters reach high abnormalities. Stage four occurs within the following four to fourteen days; during this time the outcome of the intoxication will appear. The patient will either recover or develop complete liver failure [11].

Serum ALT is routinely used in the diagnosis of hepatic injury following Paracetamol overdose, and has been validated [12] [13]. At the initial presentation, patients with Paracetamol poisoning who exhibit acute liver failure almost always have an increase in serum ALT activity, thereafter show rapid increases in ALT [12]. Diagnosis of Paracetamol poisoning is predicated on serum levels of the drug, even in the absence of symptoms. Serum level above 140 μg/mL at 4 h from ingestion is considered toxic. If the levels fall within toxic range based on the Rumack-Matthew Nomogram, then antidote treatment should commence [12].

N-acetylcyteine cysteine is used as an antidote for paracetamol toxicity. The antidote helps replenish liver glutathione level, thereby increasing the safe detoxification of N-acetyl-p-benzoquinone imine, NAPQI [14]. There are two ways of administering the antidote. First as an IV formulation for 20 hours or oral medication for 72 hours [15]. N-acetyl-cysteine administration should still be carried out in patients presenting 24 h after the ingestion of Paracetamol as it may enhance survival. Hemodialysis may also be effective, especially when concurrent renal failure exists [8].

We present a case report of Paracetamol toxicity in a malnourished child with cerebral palsy admitted in our setting and the measures taken for successful reversal of the toxicity.

2. Case Report

Five years old male child known to have Spastic Quadriplegic Cerebral Palsy with Epilepsy on Tabs Carbamazepine 200 mg 12 hrouly, Tabs Phenytoin 75 mg 12 hourly and Tabs Baclofen 5 mg 12 hourly. He was admitted in the hospital with complains of productive cough associated with difficulty in breathing and fevers. The onset was followed by non bilious vomiting that was non projectile, containing recently eaten food materials, no blood in vomit, but there were times where the vomit came out from the nostrils. He was born by normal spontaneous vaginal delivery and delayed to cry after birth. Mother is unsure of the birth weight. He is the only child to the mother and parents have separated since the mother was

pregnant. The mother is petty trader currently and leaves her child at a daycare centre for Disabled children for care.

Clinically on admission he was ill looking, febrile T- 38.7˚C, pale, not cyanosed, with lower limbs non pitting edema. Weight was 13.7 kgs, length of 105 cm. His Body mass Index (BMI) was 12.4 kg/m^2. On his respiratory system examination he had nasal flaring, symmetrical chest movement, lower chest wall indrawing with use of abdominal muscles and bilateral basal crepitation more on the right lung. His musculoskeletal examination, he had lead pipe rigidity of both upper limbs with scissoring of legs. Other systems were essentially normal. The working diagnosis was Spastic Quadriplegic Cerebral Palsy with Aspiration Pneumonia. He was started on IV Cefriaxone 350 mg 12 hourly, IV Metronidazole 130 mg 8 hourly and Paracetamol suppository 250 mg 6 hourly. He continued to use his anti convulsants as previously prescribed. On the third day in the ward after receiving 8 doses of paracetamol suppository, he started developing jaundice and he had severe vomiting more than 5 episodes per day. On examination he was drowsy, dehydrated, jaundiced, pale, with lower limbs edema. His vitals were heart rate of 153 beats per minute, oxygen saturation of 93% on oxygen, temperature of 37.1˚C, respiratory rate of 36 breaths per minute. On his abdominal examination he had slightly distended abdomen, moves with respiration, soft, not tender, hepatomegaly of 4 cm below costal margin. Laboratory investigations done showed ALT 1218 U/l, AST 197.2 U/l, Serum albumin 22.2, Serum protein 49.2, BUN 6.4 mg/dl, serum creatinine 0.25 mg/dl. Hepatitis B and C were negative. We suspected he had developed acute liver failure secondary to paracetamol toxicity. Patient was transferred to high dependent unit for monitoring. Day 6 post admission, he was vomiting coffee ground materials and jaundice had increased. On control of his liver enzymes, serum ALT 1389.3 U/l, AST (SGOT) 1809.8 U/l, Bilirubin (Direct) 4.14, Serum protein 52.4, Albumin 22.4, Prothrombin Time 28.1 sec, INR 2.24 sec. We initiated N acetyl cysteine (NAC) 1900 mg orally through the nasogastric tube STAT, then continued with 1000 mg orally every 4 hours 31 doses along with multivitamin 2 mls orally once a day, high carbohydrate diet and Ondansetron 2 mg IV 8 hourly for the vomiting. We stopped all IV antibiotics. He received the STAT dose for NAC and the next dose 4 hourly for only one day and then he did not receive the medication afterwards (mother ran out of medication). Day 7 post admission the plan was to restart the dose of NAC as 1900 mg orally STAT then 1000 mg orally every 4 hours and added Pantoprazole 8mg IV once a day. He was feeding high carbohydrate diet as planned by nutritionist, calculated at 170 mls using the perfusor every 3 hours. From day 7 post admission after adhering to NAC administration, jaundice was reducing however he was still vomiting when fed 150 mls of high carbohydrate diet at once and he had bilateral lower limbs pitting edema and sacral edema. We decided to revise the nasogastric tube and start feeding him with F 75 due to the Underweight and edema, and to control electrolytes where he had mild hypokalemia of 3.2 mmol/l and he was given Slow K (oral Potassium Chloride) 5 mEq 12 hourly for

5 days which raised his potassium levels to 4.8 mmol/l.

Following initiation of F 75 he had no further episodes of vomiting, jaundice and lower limbs edema were reducing and on day 8 he finished the NAC doses. On day 9 the liver enzymes were controlled and they were dropping compared to previous levels, AST 90.9 U/l ALT 218 U/l, serum albumin 30, and serum protein 66.4. He progressed well in the ward, the jaundice and edema had resolved on day 14 post admission. Control liver enzymes were ALT 6.1 U/l, AST 19.3 U/l, Bilirubin 0.3, Albumin 23.3, and Protein 53.8. He was discharged with instructions for high protein diet and he will be on follow up clinic.

3. Discussion

Most common cause of acute liver failure in the world is liver toxicity caused by Paracetamol due to an increased use of IV Paracetamol in hospital setting in children who cannot tolerate oral medications [2]. Our patient received rectal Paracetamol at 250 mg 6 hrly (18 mg/kg/dose) but we had not factored in the child had malnutrition as literature shows the glucuronidation capacity of the liver is less in malnourished individuals due to their low carbohydrate stores and low glutathione stores making them more susceptible [10].

The recommended diagnostic marker for initiating therapy is serum levels of the Paracetamol. Serum level above 140 μg/mL at 4 h from ingestion is considered toxic. If the levels fall within toxic range based on the Rumack-Matthew Nomogram, then antidote treatment should commence [12]. In our setting we do not have the ability to do serum levels of drugs and hence relied on liver function tests, Prothrombin time, INR and clinical features which all marked our patient to be in Stage 3 or 4 of liver failure hence we initiated therapy early.

In patients with acute ingestion and have presented within an hour of poisoning with the drug, gastrointestinal decontamination may be carried out with the use of activated charcoal in unconscious patients. However, the use of whole bowel irrigation or orogastric lavage has been reported to be ineffective [8] [16]-[18]. In our patient we did not do lavage but initiated NAC which after 4 days the liver functions reduced. There was a time period where medication ran out after 24 hours and the treatment and to be re initiated from the beginning. NAC helps in replenishing liver glutathione level, thereby increasing the safe detoxification of N-acetyl-p-benzoquinone imine, NAPQI [8], it also works by preventing NAPQI from binding to macromolecules of the liver, acting as a replacement for glutathione, sulfate precursor, and can reduce NAPQI back to acetaminophen [14]. It is recommended to be used when serum drug levels are within the range of toxicity or when a dose of acetaminophen above 140 mg/kg was ingested at time greater than 8 h; and ingestion showing any symptoms of hepatotoxicity [19].

4. Conclusion

Paracetamol is a commonly used drug especially among Paediatric patients with potential for overdose. Paracetamol poisoning can lead to liver failure with possi-

ble fatal development in children. Reversal of Paracetamol toxicity is dependent on early identification with early initiation of appropriate medication. We advocate for increased awareness among clinicians on appropriate dosage of Paracetamol specific to the type and nutritional status of the individual.

Ethics Approval and Consent to Publish

Written informed consent was obtained from the patient's parents for writing of this case report

Consent for Publication

Written informed consent was obtained from the patient's parents for publication for this case report

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Author Contributions

All authors made a significant contribution to the work reported and gave final approval for the publication of the version.

Disclosure

The authors declare they have no competing interests. All authors of the manuscript have read and agreed to its contents.

Conflicts of Interest

The authors declare no conflicts of interest.

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass Index
BUN	Blood Urea Nitrogen
INR	International Normalized Ratio
NAC	N-acetyl-cysteine
NAPQI	N-acetyl-p-benzoquinone imine