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Acute Liver Failure in a 10 Months Old Male after Repeated Therapeutic Dosage of Paracetamol

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ABSTRACT

Severe hepatotoxicity caused by paracetamol is not common in infants after administration of therapeutic dose. We report a case of paracetamol-induced acute liver failure in a 10 months old infant after repeated therapeutic dosage of paracetamol.

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Introduction

Paracetamol (N-acetyl-p-aminophenol) is a widely used analgesic and antipyretic in children; however, toxic exposures are rare in infants. The toxicity of paracetamol overdose has long been recognized. Potentially toxic doses are those that are greater than 150 mg/kg/dose in children and greater than 7–10 g/dose in adult [1]. With the advent of many combination analgesic medications, the potential for unintentional overdose has increased [2]. In the United States, two concentrations of liquid formulations of acetaminophen for infants are now available, further increasing the risk of incorrect dosing [3]. Paracetamol hepatotoxicity is caused by the formation of a toxic metabolite, N-acetyl-p-benzoquinone mine (NAPQI). When acetaminophen is used in therapeutic doses, most of the drug is metabolized via glucuronidation and sulfation; a very small amount of acetaminophen is metabolized to NAPQI by the hepatic enzyme cytochrome P450 2E1 (CYP2E1) [4]. N-acetyl-p-benzoquinone mine is then conjugated by glutathione to form the benign metabolite, mercapturic acid, which is excreted in the urine. The potential for hepatotoxicity develops when large doses of acetaminophen saturate the typical conjugation pathways and overwhelm available glutathione stores, leading to reduced clearance of the toxic metabolite. Accumulation of the toxic metabolite can then exert untoward effects on key cellular structures and functions the ability of the liver to metabolize paracetamol changes with age owing to differences in activity of these key metabolic pathways. Although the mechanism of acetaminophen toxicity is well recognized, the clinical implications of age-related differences and the ontogeny of hepatic pathways may not be commonly appreciated. When taken in normal therapeutic doses, paracetamol has been shown to be safe [5]. Following a therapeutic dose, it is mostly converted to nontoxic metabolites via Phase II metabolism by conjugation with sulfate and glucuronide, with a small portion being oxidized via the cytochrome P450 enzyme system [6]. Cytochromes P450 2E1 and 3A4 convert approximately 5% of paracetamol to a highly reactive intermediary metabolite, N-acetyl-p-benzoquinone imine (NAPQI) [5-9]. Under normal conditions, NAPQI is detoxified by conjugation with glutathione to form cysteine and mercapturic acid conjugates [6,10]. The concentration of a drug attained after a single dose depends on its volume of distribution, which in turn depends on the volume of plasma and tissue and on the fractions of unbound drug in plasma and tissue. After multiple dosing, mean SteadyState concentrations reflect the dose and dosage interval, clearance, and bioavailability. Total clearance is based on the sum of the partial metabolic and renal clearances. Some pharmacokinetic parameters such as clearance, volume of distribution and bioavailability are age-related. This affects the dose and dosage interval needed to maintain therapeutic concentrations. The present study described a new case of liver failure in 10 months infant after repeated doses of paracetamol, treated successfully with N-acetyl cysteine.

Case Description

Male patient, 10 months old, weighing 8.6 kg , son of consanguineous parents, arrived to our emergency department with a history of irritability, refusal to eat for 4 days, frequent vomiting for the last 4 days, abdominal distension and slight respiratory distress and frequent loose motion for the last 4 days about 10-11 times per day. At the day of presentation he started to shows more irritability, vomiting of blood and had bloody diarrhea. Before admission, the child was seen many times in private clinic receiving there intravenous fluid for rehydration. The mother reported having administered paracetamol orally (15mg/kg/dose every 4 hours for 3 consecutive days - total dose of approximately 90mg/kg, according to previous prescription to him by private clinic doctor, claiming that, for the last 4 days the baby was “feverish”. At admission (D1), the child was afebrile, irritable at first then after about 4 hours he became drowsy with signs of shock (heart rate - HR=183bpm, slow capillary refill, weak pulse, mottled skin), jaundice, hepatomegaly and massive upper gastrointestinal bleeding. The main laboratory findings obtained in the first 24 hours of admission included coagulopathy (incoagulable international normalized ratio – INR:4.98, activated partial thromboplastin time – APTT:58.5 sec, and prothrombin

time PT:55.2), metabolic acidosis (pH 7,20; bicarbonate 8mEq/L;), AST:1071U/L, ALT - 2U/L and hyperbilirubinemia (total bilirubin – 30.21 umol; direct – 23.5umol/l). During hospitalization, there was a progressive fall in hemoglobin levels: D1 – 11.1g/dl. D2- 9.2 g/dl. D3- 8.9 g/dl. Serum concentration of paracetamol (approximately 36-48 hours after the last dose) was of 177mcg/mL (therapeutic range of 10-20 mcg/mL, spectrophotometric method). Supportive measures included: volume replacement, serial transfusions of fresh frozen plasma, empirical antibiotic therapy (ceftriaxone,vancomycine and acyclovir),kept NPO, potassium chloride and phosphate, N-acyetylcysteine IV (As advised by poisoning center) and lactulose by NGT (nasogastric tube) . After laboratory confirmation of toxic exposure to paracetamol, the protocol of continuous intravenous infusion of N-acetylcysteine in 36 hours was introduced (150mg/kg in 60 minutes; 50mg/kg in 4 hours; 100mg/kg in 16 hours), maintained at 6.25mg/kg/hour until D4. Given the severity of the case and the possibility of progression to liver transplantation. During evaluation, there was a progressive decrease of aminotransferase concentrations and improvement of coagulation; infusion of N-acetylcysteine was suspended on D4 [3].

Table 1: Main Laboratory Findings During Hospitalization

DAY(D)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D13
ALT(RV<15U/L)	2	2	240	631	2174	1823	NP	1187	1135	366
AST(RV<30U/L)	1071	2092	726	581	431	269	NP	142	108	62
Total Bilirubin (RV 5-20.5UMOL/L)	30.21	36.7	31.3	19.9	25	13.6	NP	12	9.42	12.3
Direct Bilirubin (RV1.7-8.6UMOL/L)	23.5	19.6	14.3	17	15	6.1	NP	6.7	5.79	3.3
Paracetamol (RV 10-20 mcg/ml)	177	NP	NP	NP	NP	88	NP	NP	NP	NP
INR(RV0.9-1.1) 3.88	4.98	1.6	1.15	1.21	1.16	NP	0.95	0.96	0.96	0.98
Albumin(RV34-50G/L)	24	25	25	20	23	25	NP	NP	28.8	36
Potassium(RV>3.5)	3.1	2.8	3.1	3.6	5	4.7	NP	5	5.2	NP
Haemoglobin(RV>11.1)	11.1	9.2	8.9	8.8	9.5	9.4	NP	9.5	NP	NP
Ammonia (RV<28UMOL/L)	86.8	NP	42.6	NP	NP	NP	NP	NP	NP	NP
Lactic Acid(RV 0.5-2.2)	3.2	NP	NP	NP	1	NP	NP	NP	NP	NP

ALT: Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **RV:** Reference Values; **TR:** Therapeutic Range; **INR:** International Normalization Ration; **NP:** Examination Not Performed.

In the screening of viruses that can cause liver failure hepatic virology testing for HAV , HBV, HCV SEROLOGY done and all came to be negative. Metabolic screening for galactosemia, tyrosinemia, and organic acidemia was negative. Maternal serological testing for HIV, toxoplasmosis, syphilis, and hepatitis B and C were also negative. The outpatient follow-up undertaken for 6 months showed complete clinical and laboratory recovery and adequate neuropsychomotor development.

Discussion

In general, the time of peak absorption following ingestion of paracetamol is rapid (30-45 minutes), with analgesic and antipyretic action achieved with serum concentrations of 10 and 4-18Î1/4g/mL, respectively, including in children. About 90% of paracetamol is conjugated in the liver (glucuronidation - 40-67%; sulfation - 20-46%), forming inactive metabolites excreted in the urine. Approximately 5-15% of the drug is oxidized in the CYP2E1 and, to a lesser extent in the CYP2A6, CYP1A2, and CYP3A4, resulting in the formation of toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which readily combines with glutathione, turning into nontoxic cysteine/mercaptate conjugates eliminated in urine. The hepatotoxic action of paracetamol is associated primarily to the activity of the CYP2E1 enzyme system and the production of NAPQI [11]. In overdoses with clinical repercussion, by isolated overdoses or after supratherapeutic doses, the maximum rates of glucuronidation and sulfation are reached and the availability of glutathione is insufficient to metabolize NAPQI. Then, the free NAPQI binds covalently to hepatic proteins of the cysteine group, triggering hepatotoxicity and cell death [11,12]. Acetaminophen-protein products, such as 3-(cysteine-S-yl)-paracetamol-adduct are released into the blood after hepatocyte lysis. They are measured by high performance liquid chromatography with electrochemical detection and may be used as specific biomarkers of hepatotoxicity, even several days after the exposure [12]. A study in adults who developed liver failure induced by paracetamol overdoses showed a positive correlation between the serum concentration of acetaminophen-protein adducts and severity of hepatotoxicity, which can be detected up to 12 days after ingestion [12]. In contrast, the pharmacokinetics and pharmacodynamics of paracetamol in neonates and young infants (under 1 year) differ substantially from older children and adults. The combination with glucuronides is immature, while sulfation is well developed, consisting in the main metabolic pathway [10-15]. The clearance of paracetamol in term neonates is decreased and the half-life is prolonged compared to that of adults (approximately 3.5 versus 1.9-2.2 hours), so a distinct dosage is recommended (20mg/kg/dose, every 8 hours, no longer than 48 hours of use), due to the risk of toxicity of cumulative doses [10,15]. In addition, the elimination half-life of paracetamol may be extended further after multiple doses, in poisoned patients and in those who develop liver failure [10,11,13,15]. Although the rates of metabolism of CYP2E1 were decreased and the ability to generate glutathione, increased, providing greater protection after isolated overdoses, neonates may also produce toxic metabolites (NAPQI), triggering up hepatotoxicity and cell lysis if glutathione reserves are depleted [10,11,14,15]. It should be noted that paracetamol-protein products could also be used as specific biomarkers of hepatotoxicity in children, especially to assist the diagnosis of acute liver failure of unknown etiology [14].

Even considering the background of the mother, which could raise doubts about the actual dose, the continuous use of medication for 3 days, the possible additional doses transferred through breast milk, and the high serum paracetamol levels detected established a causal relationship between prolonged use drug and liver failure. Reinforcing these findings, Penna and Buchanan described in their review the cases of two young infants, 6 to 7 weeks of life, who also developed severe hepatotoxicity after ingesting repeated doses of paracetamol (approximately 100mg/kg/day/2 days and 60mg/kg/day/6 days, respectively) [15].

N-acetylcysteine is the antidote of choice in the treatment of acetaminophen poisoning, being a precursor of reduced glutathione, which, when given early, can prevent liver damage induced by paracetamol, restoring glutathione levels [12,16,17]. When the moment of exposure is known, the administration of N-acetyl cysteine is formally indicated after ingestion of isolated overdoses of paracetamol, when the serum levels, preferably obtained between 4 and 8 hours of ingestion are above the possible risk line on the Rumack-Matthew nomogram, even without clinical or laboratory evidence of liver injury [12,16]. When the time of exposure is unknown or it is not possible to get the serum concentration levels within 8 hours of exposure, but the estimated dose is above 200mg/kg in the last 24 hours (or ≥10g in adolescents and adults), the use of N-acetylcysteine is also indicated, and the decision about the suspension of treatment is based on clinical and laboratory progress [12-18].

Other more complex situations involve the indication of N-acetyl cysteine after prolonged or supratherapeutic use of paracetamol, when assessing the risk of hepatotoxicity by the Rumack-Matthew nomogram is not possible [12,16,17,19]. In general, it is recommended the use of N-acetyl cysteine when the serum concentration of paracetamol is above 10μg/mL or AST>50UI/L [12,16,19]. In patients with liver failure, as described, N-acetyl cysteine also possibly acts as an antioxidant, improving hemodynamics, oxygen consumption, and cerebral edema [17]. Patients with paracetamol-induced liver failure, either by isolated overdoses or by supratherapeutic doses, should be given intravenous N-acetyl cysteine until the encephalopathy resolves itself or until they present significant improvements in the results of ALT, INR, and creatinine or until liver transplantation [16,17]. In the present case, continuous intravenous infusion of N-acetyl cysteine proved to be effective, safe, and without adverse effects, even in prolonged use. Although studies in experimental models suggest that carnitine deficiency, as a cause or consequence, may be associated with hepatotoxicity triggered by acetaminophen it would be speculative to infer this association only with the data available in the present report (a single measurement during the course of liver failure). Clinical studies are needed to define and characterize the association more accurately. However, it can be inferred that the laboratory screening, the evolution, and the outpatient follow-up practically exclude the possibility of genetic diseases associated with changes in the carnitine transport and the carnitine cycle, which can evolve with liver failure [20,21].

Conclusion

It is possible to conclude that the continued use of acetaminophen can cause severe hepatotoxicity in infants. The specific dosage for infants should be followed, avoiding the continuous use for more than 2 to 3 days [10,15].

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References

1. Blackford MG, Felter T, Gothard MD, Reed MD (2011) Assessment of the clinical use of intravenous and oral N-acetylcysteine in the treatment of acute acetaminophen poisoning in children: a retrospective review. Clin Ther 3: 1322-1330.
2. Fontana RJ (2006) "Unintentional" acetaminophen overdose on the rise: Who is responsible? Dr. Robert J. Fontana is interviewed by Paul C. Adams. Can J Gastrointerol 20: 319-324.
3. United States Food and Drug Administration Addition of another concentration of liquid acetaminophen marketed for infants (2011) Rockville (MD): The Administration www.fda.gov/Drugs/DrugSafety/ucm284741.htm.
4. Zhao L, Pickering G (2011) Paracetamol metabolism and related genetic differences. Drug Metab Rev 43: 41-52.
5. Heard KJ (2008) Acetylcysteine for Acetaminophen Poisoning. The New England Journal of Medicine 359: 285-292.
6. Sweety Mehta (2012) Metabolism of Paracetamol (Acetaminophen), Acetanilide and Phenacetin Sweety Mehta | Medicinal Chemistry, Notes, Pharmacology https://pharmaxchange.info/2012/08/metabolism-of-paracetamol-acetaminophen-acetanilide-and-phenacetin/.
7. Richardson JA (2000) Management of acetaminophen and ibuprofen toxicoses in dogs and cats (PDF). Journal of Veterinary Emergency and Critical Care 10: 285-291.
8. Rumbeiha WK, Lin YS, Oehme FW (1995) "Comparison of N-acetylcysteine and methylene blue, alone or in combination, for treatment of acetaminophen toxicosis in cats". American journal of veterinary research 56: 1529-1533.
9. Corcoran GB, Mitchell JR, Vaishnav YN, Horning EC (1980) Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. Molecular Pharmacology 18: 536-542.
10. Mitchell JR, Jollow DJ, Potter WZ, Gillette JR, Brodie BB (1973) Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. The Journal of Pharmacology and Experimental Therapeutics 187: 211-217.
11. Hendrickson RG (2011) Acetaminophen. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's toxicologic emergencies. 9. New York: McGraw-Hill 483-499.
12. James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, et al. (2009) Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 37: 1779-1784.
13. Roberts I, Robinson MJ, Mughal MZ, Ratcliffe G, Prescott LF (1984) Paracetamol metabolites in the neonate following maternal overdose. Br J Clin Pharmacol 18: 201-206.
14. Lederman S, Fysh WJ, Tredger M, Gamsu HR (1983) Neonatal paracetamol poisoning: treatment by exchange transfusion. Arch Dis Child 58: 631-633.
15. Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH (2022) Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology 96: 1336-1345.

16. AW MM, Dhawan A, Baker AJ, Mieli-Vergani G (1999) Neonatal paracetamol poisoning. Arch Dis Child Fetal Neonatal Ed 81: 78-78.
17. Heard KJ (2008) Acetylcysteine for acetaminophen poisoning. N Engl J Med 359: 285-292.
18. Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, et al. (2006) Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 44: 1-18.
19. Daly FF, O'Malley GF, Heard K, Bogdan GM, Dart RC (2004) Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med 44: 393-398.
20. Arafa HM (2009) Carnitine deficiency: a possible risk factor in paracetamol hepatotoxicity. Arch Toxicol 83: 139-150.
21. Longo N, Amat di San Filippo C, Pasquali M (2006) Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin Med Genet 142C: 77-85.