Review Article

Exploring the Efficacy of N-Acetylcysteine as a Novel Treatment for Acetaminophen or Paracetamol Toxicity in Pediatrics: A Comprehensive Review

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ABSTRACT

Acetaminophen or Paracetamol is well known for its antipyretic and analgesic properties. As it has both analgesic and antipyretic properties, it is mostly preferred over other analgesics and antipyretics. It is a commonly used analgesic and antipyretic agent in children. It is being used in children in various dosage forms like syrup dosage forms or tablet dosage forms according to their age. And when any drug is being administered to children, it is the most concerning matter. If Acetaminophen or Paracetamol is administered in proper dose, it does not cause any unintended effect in children. But it can be heavily dangerous if it is being used too much. When the dose is a little high or somehow the child takes too much of the medication, it can cause drug overdose, basically it can be said that Acetaminophen or Paracetamol overdose which in turn can cause drug induced toxicity. This toxicity in children may lead to hospitalization and even death. Over the years, after cosmetic induced health problems, Paracetamol toxicity remains the most common problems which can be seen everywhere around the whole world. Though the symptoms are not obvious, some of the most common symptoms of Acetaminophen or Paracetamol toxicity are:

i) Nausea and vomiting, ii) Drowsiness, iii) Loss of consciousness, etc.

The treatment of the Paracetamol or Acetaminophen toxicity varies and it's mainly depending on the seriousness of the condition. N-acetylcysteine is used for the toxicity caused by Acetaminophen or Paracetamol overdose and can be administered orally or intravenously.

Keywords: Acetaminophen, Pediatrics, Hepatotoxicity, N-Acetylcysteine, Paracetamol.

INTRODUCTION

Analgesic and antipyretic drugs are being used over the years in all age groups. Among those drugs, Acetaminophen or Paracetamol is consumed around the world as it has good analgesic and antipyretic properties. It is being sold in the market as a prescription medication or as a non-prescription medication (OTC Drugs-Over the Counter Drugs) [1].

Metabolism of Acetaminophen or Paracetamol at Therapeutic Doses: Acetaminophen or Paracetamol is metabolized in liver mostly. However, kidney and intestine also take part in Acetaminophen or Paracetamol metabolism [3]. After taking the proper dose of Acetaminophen, Acetaminophen is converted into pharmacologically not active product glucuronide and conjugate of sulphate, a very small amount of which undergoes oxidation reaction and produce metabolically active product N-acetyl-p-benzoquinone imine (NAPQI, also called as NAPBQI) [2,3]. It is produced in very small quantity. This NAPQI product causes toxicity. The activity of NAPQI is masked by attaching to the sulfhydryl group of glutathione which leads to formation of Acetaminophen-Glutathione complex and excretion occurs through urine as Acetaminophen-Cysteine complex [1,2,3]. A little amount of Acetaminophen-Glucuronide complex and Acetaminophen-sulphate may present in bile [2,3].

Uridine 5'-diphospho-glucuronosyl transferase (UDP-UGT) catalyzes Paracetamol glucuronidation [1,2]. Acetaminophen becomes more hydrophilic by the action of UGTs; the UGTs remove the glucuronosyl group from Uridine 5'-diphospho-glucuronic acid [1,2,4]. Human liver microsomes have various enzymes for drug metabolism. Research studies on these human liver microsome and liver cells have shown that UGT1A1, UGT1A6, UGT1A9 and UGT2B15 are involved in Acetaminophen glucuronidation [2,5-8].

Sulfotransferases takes part in Acetaminophen or Paracetamol sulfation. Enzymes of Cytochrome P450 take part in Paracetamol oxidation and the metabolically active product N-acetyl-p-benzoquinone imine (NAPQI or NAPBQI).

Metabolism of Acetaminophen at Highly Toxic Doses: When Acetaminophen is administered at the maximum level, the sulfation pathway exceeds, but glucuronidation and oxidation of Acetaminophen rise high and a little amount of Paracetamol is eliminated in unmodified form [2,3]. At administration of Acetaminophen at highly toxic doses, glucuronidation also exceeded and the elimination of Paracetamol in unmodified form also increases. As the NAPQI or NAPBQI also increases, glutathione stores are

exhausted [2,4]. The NAPQI mainly attached to proteins of mitochondria and ion channels which in turn decrease or dropping of production of energy, electrolyte imbalance, and even the cells die [1-3,9].

Pharmacokinetics of Acetaminophen: Acetaminophen is a lipophilic drug and absorbed in the gastrointestinal tract (peak drug concentration [Tmax] 0.5-0.75 h after the consumption of the drug orally), and bioavailability is around 90% [10-14]. pKa of acetaminophen is 9.5 which show that it has less absorption in stomach [14,15]. But it is absorbed in the duodenum more quickly and reach the blood circulation [14,15].

Metabolism of acetaminophen occurs in the liver mainly. In case of an adult the amount of glucuronide and sulphate conjugates are 50-60% and 25-30% respectively, and less than 10% are excreted as an unchanged form [10,14,16]. In case of children, the metabolism of acetaminophen remains same, but the sulfation pathways develop at the time of birth and the glucuronidation pathways develop at 2 years of age [10,14,16]. In children, 90% of acetaminophen molecules are excreted as an unchanged form through urination in just 24 h [14-19].

Pharmacodynamics of Acetaminophen:

Acetaminophen suppresses COX and brings down the prostaglandin synthesis by acting at the peroxide site [14,20,21].

Drug Profile of N-Acetylcysteine: N-acetylcysteine, NAC is not costly and available in the market [22]. NAC is not available in natural resources, but availability of cysteine is seen in meat, egg [23].

Administration of N-Acetylcysteine in Acetaminophen Toxicity: The NAPQI or NAPBQI is a metabolically active product; glutathione can reduce the amount of NAPQI [24]. NAC increases glutathione which in turn help to decrease NAPQI IN mitochondria and the sulfation pathway is also intensified [1,2].

LITERATURE REVIEW

In the WHO Model List of Essential Medicines for 2019 intravenous formulation is listed of acetylcysteine which is 200 mg/ml in 10 ml ampoule. Adult or children in both cases, the dose is 150 mg/kg IV within 15 minutes, after that a dose of 50 mg/kg within 4 hours and thereafter 100 mg/kg within 16 hours. Dosing of NAC depends on patients age [25].

Prescott, et al. 1979, worked on the use of intravenous NAC to treat acetaminophen toxicity in 100 patients. The ages of the patients (in years) were between 13-82 years and mean age (in years) was 33. Out of 62 patients, only one who was treated between 10 hours of up taking acetaminophen showed toxicity in liver. Patients who were administered NAC within 10-24 hours (mean 15 hours) of up taking show hepatotoxicity of 53%. No deaths reported in patients who were administered in not more than 10 hours. According to their report, drug induced toxicity in liver was 52-58% (3 deaths) [26].

Rumack and his co-workers reviewed the use of N-acetylcysteine. 2 patients who were below the age 5 showed toxic APAP levels, 78 patients were of 12-21 years, 20 patients were adults. Of all these patients, 49 patients did not have any hepatotoxicity as they had started the treatment with NAC in between 10 hours. Those patients whose NAC therapy was late and were treated with NAC after more than 10 hours had hepatotoxicity (45% cases) [27]. The two patients who were below the age 5 did not have hepatotoxicity. The same researchers worked on the oral use of NAC in 662 patients, out of them 23 patients were below the age of 13. All the patients of all ages were treated with oral NAC in between 10 hours of taking APAP and there was a 7% case of hepatotoxicity. For the patients who were treated within 10-16 hours, more than 24 hours had 29% and 62% cases of hepatotoxicity respectively [28].

Bebarta, et al. 2010, worked on the route of administration of N-acetylcysteine for acetaminophen overdose over 503 patients. 306 patients (61%) were administered intravenous acetylcysteine for their complete course, the age of the patients were between (23-45 years). 145 patients (29%) were administered acetylcysteine orally for their complete course, the age of the patients were between (23-45 years). The route of administration of 52 patients (10%) who were initially administered acetylcysteine orally or intravenously was changed. Out of 52 patients, 19 patients who were treated with IV NAC were shifted to oral NAC, 28 patients who were administered NAC orally were shifted to intravenous NAC administration and 4 patients who were given oral administration of NAC firstly were shifted to IV NAC and then redirected to oral NAC, 1 patient whose primary route of administration was unknown was given intravenous NAC. The duration of treatment for only-oral administered group was 31.4 (20.4 to 50.7) hours and for only-IV administered group was 26.4 (13.2 to 52.0) hours and 47.5 (31.7 to 79.5) hours in both group. Around 90.3% of the patients remain alive and did not have any liver transplantation future, 0.4% had to go for liver transplantation, 5.2% of the patients died and 4.2% showed unspecified results [29].

Akin, et al. 2011, studied cases on hospitalization of the children who were intoxicated and found that 72.1% children of the total patients were admitted due to intoxication. Out of 72.1% children, 4% children were admitted due to acetaminophen poisoning [30].

Blackford, et al. 2011, reviewed the clinical use of IV and oral use of NAC in the treatment of acetaminophen poisoning in children. 37 patients (60%) of the total patients (62) were treated with IV NAC and 25 patients (40%) of the total patients (62) received oral NAC. The treatment of IV NAC was given for average 23.6 hours (for 17.6- 54.9 hours). The treatment of oral NAC was given for 69.5 hours (for 33-133 hours). They reported that 3 patients treated with extended NAC therapy and also

concluded that patient-related factors should be observed[31].

Ogilvie, et al. 2012, reviewed the cases of acetaminophen overdose and reported that N-acetylcysteine was effective for acetaminophen overdose and also included that the best route for administering NAC was not proven [32].

Bond, et al. 2012, analyzed the various trends in hepatic injury caused due to accidental overdose of paracetamol (acetaminophen) in products with and without opioid. In case of paracetamol opioid combination, 119731 cases were reported, out of which in 8995 cases, the patient was treated with NAC. Only 2.3% patients had hepatic injury. 126830 cases were reported due to use of paracetamol without opioid, out of which in 15706 cases, the patients were treated with NAC and only 3.7% patients had hepatic injury [33].

Ozenir, et al. 2013, studied the demographic factors, family factors which affected the prediction of drug poisoning in childen , found that 1.23% of the total cases of hospital admission of children were due to drug poisoning and also reported that paracetamol poisoning cases were around 13.8% [34].

Kelly Williamson, et al. 2013, studied the various routes of administration and time of administration of NAC for APAP toxicity. Out of 4642 cases of APAP overdose, total 795 patients were administered NAC. Out of 795 cases, 213 patients were treated with 20-hour IV NAC, their ages were between (22-26 years). 213 patients were treated with 36-hour oral NAC, their ages were between (23-29 years), and 369 patients were treated with 76-hour oral NAC, their ages were between (25-28 years). The mean 4-hour acetaminophen concentration was 199 µg/ml, 114 µg/ml, 205 µg/ml respectively. No patient needed transplant and no death was reported. They also concluded that if NAC was administered within 8 hours of APAP toxicity, 20-hour IV NAC could work the same as the longer 36-hour oral NAC and 72-hour oral NAC [35].

Lars E Schmidt, et al. 2013, worked on the risk factors of anaphylactoid adverse effects to intravenous NAC and studied individual patients with particular risk factors. Total 1218 cases were reported due to paracetamol overdose. Out of them 950 patients were administered IV NAC, 18.6% cases showed Anaphyloid adverse effects. The number of cases with adverse effects decreased from 25.9% in cases with undetectable p-paracetamol to 6.3% in cases with p-paracetamol above 226 µg/ml [36].

K Heard, et al. 2014, conducted a multicenter, single arm, open label clinical trial. The patients were administered 140 mg/kg loading dose and then 70 mg/kg of NAC in every 4 hours for 12 doses in between 24 hours of acetaminophen ingestion. 409 patients took part in the clinical trial process, out of which 309 patients were chosen for the analysis of the treatment. Hepatotoxicity appeared in 18.1% patients and 3.4% of patients were treated with in NAC between 10 hours of hepatotoxicity. Adverse events were seen in 28.9 % of the participating patients. Mild type of adverse events occurred which were treatable and no serious type of adverse effects were there[37].

James B Mowry, et al. 2015, analyzed the case data from National Poison Data System. Total 2890909 cases were reported in 2014, this included human exposures, animal exposures, human non-exposures, animal non-exposures. There were top 5 substance classes which were greatly involved in human exposures, analgesics (11.3 %) were one of them. In case of children who were 5 years age or less than 5 years age, analgesics (9.3%) were involved in exposures in child. In case of 1835 human exposures, death occurred [38].

R Carroll, et al. 2015, worked on the collected data on all cases of acetaminophen overdosing and reported that adult self-overdosing cases were 44%. 26.9% patients were treated with NAC therapy and if recent guidelines were followed that would increase the number to 32.6%. Anaphylactoid reaction due to treatment with NAC appeared in 22.5% of patients. They also reported that patients having acetaminophen in blood above 200 mg/L after 4 hours of ingestion of acetaminophen had huge chance of constant self-harm [39].

Karaman, et al. 2016, conducted an evaluation process on the patients who were admitted to the hospital due to acetaminophen toxicity. 44 patients were admitted due to acetaminophen toxicity, out of them 29 patients were shifted to the observation unit and 15 students were admitted to the critical care unit. The patients of critical care unit had higher paracetamol dose than the observation unit patients. 14 patients of critical care unit and 12 patients of observation unit were treated with NAC therapy. The age, sex and additional drug usage were same for both unit patients. When they observed the data of the antidote receiving patients and compared it with the patients who did not received the NAC therapy, the APAP dose and length of hospitalization were higher in patients received NAC therapy than those who did not receive. They concluded that in case of acetaminophen toxicity treatment, laboratory data were not that much important and IV NAC therapy should be considered as an antidote for its lowering effect in patients having acetaminophen toxicity [40].

David G Cairney, et al. 2016, analyzed the relationship between higher plasma acetaminophen concentration and acute liver injury.The patients were admitted to hospital for acetaminophen toxicity and were given NAC therapy within 24 hour. Acute liver injury and hepatotoxicity were usually occurred in the patients with higher plasma acetaminophen concentration and even seen in patients who were given NAC therapy within 8 hours of overdose. They also concluded that the IV dose of NAC was too low according to higher plasma acetaminophen concentration[41].

Geoffrey K Isbister, et al. 2016, conducted a observational study of a 2-phase NAC therapy. According to the protocol,

the first dose was 200 mg/kg within 4-9 hours depends on ingestion time and the second dose was 100 mg/kg in between 16 hours. In case of 654 acetaminophen poisonings, the new protocol was followed. The age of patients was between (15-98 years). In 64% cases NAC therapy was ceased due to low level of acetaminophen concentrations. 35% patients had adverse reactions, 26.5% patients had GT related systemic hypersensitivity reactions, 8% patients had skin related systemic hypersensitivity reactions, 0.5% patients had severe anaphylaxis. 48% of patients had adverse reactions who had received the complete NAC therapy as compared to 28% of patients had adverse reactions whose treatment was stopped early [42].

Yakup Yesil, et al. 2018, worked on acetaminophen overdose in children and their treatment with N-acetylcysteine. The age of the patients were between 1- 17 years and out of them 58% were female. The weight of the patients was between 9-80 kg. The time from ingestion to administration was between 0.5-20 hour. The dose of acetaminophen was between 24 -300 mg/kg. 41% patients were administered NAC therapy and decontamination therapy, where 59% patients were treated with only decontamination therapy. 64% patients had symptoms like nausea, abdominal pain, where 36% patients were asymptomatic [43].

Helene Salmonson, et al. 2018, worked on 53 cases, the ages of the patients were between 13-68 years and the mean dose was 20g (between 10-166). The total numbers of females were 74%. 10 patients had constant high serum levels for ≥24 hours, out of them 6 patients had a second peak 8-19 hours after ingestion. 34 patients treated with NAC therapy within 8 hour. 7 patients out of them had greater amount of alanine aminotransferase. 3 patients out of them had hepatotoxicity [44].

Monica Abadier, et al. 2019, reported a case of a neonate (10 days old) who was admitted to the hospital after acetaminophen overdose. Acetaminophen concentration was 381 µmol/h after 19.5 hour of last dose of Acetaminophen and 236 µmol/h after 9 hours later. Alanine aminotransferase was normal and total bilirubin amount was 262 µmol/L (N< 300). Acetylcysteine therapy was started and stopped after 24 hours when serum paracetamol level was unnoticeable. When serum serum paracetamol metabolites level were checked initially, it was 64% of total metabolites, after administering NAC, serum bilirubin level increased and paracetamol–sulphate concentration was 72% of total metabolites. They also concluded that constant paracetamol ingestion increased the elimination half life [45].

Cristian Locci, et al. 2021 reviewed a total of 27 case reports, many review articles and other related papers and reported that neonatal acetaminophen poisoning resulted from maternal acetaminophen overdose. Newborns and infants who had a single overdose and had paracetamol concentration below Rumack-Mathew nomogram limits were at low risk and those who were treated with more than one supratherapeutic dose of acetaminophen should be monitored, N-acetylcysteine could be considered as a specific antidote and should be administered according to weight of patients [46].

DISCUSSION

Analgesics are the most commonly used drugs. Acetaminophen or paracetamol toxicity is very common in all ages. Acetaminophen toxicity can happen accidentally or intentionally. When the dose of Acetaminophen or Paracetamol is more than the therapeutic dose, it can cause toxicity. To treat this condition, oral and intravenous acetylcysteine are both effective and safe. The route of administration should be chosen based on the physician and patient preference. If the NAC therapy is started earlier, it can stop the toxicity caused by acetaminophen paracetamol. After starting NAC therapy, most of the patients do not need any organ transplant mostly liver transplant. Adverse effects related to acetaminophen are not very much serious. Out of them most commonly seen adverse effects are nausea, vomiting, headache, abdominal pain. Very few patients have anaphylactoid reactions. This NAC therapy depends on some patient related factors like age, weight and also be affected if the patient has any disease previously. The duration of the treatment will vary according to the patient's condition.

CONCLUSION

Acetaminophen toxicity is very common type of toxicity. N-acetylcysteine should be preferred for the treatment of acetaminophen or paracetamol toxicity in children. Both oral and intravenous routes of administration are considered and both are equally effective. Both Oral and intravenous routes of administration are well tolerated. Oral route is preferred initially, but if the patients have a tendency of vomiting or the patients are having constant vomiting IV NAC is administered. If the toxicity of APAP is recognized at early stage, hepatotoxicity can be prevented. But to obtain an appropriate level of APAP, NAC should be administered within 8 hours of ingestion of APAP. The initiation of NAC therapy should be done as soon within the time of ingestion of APAP as late treatment increases the possibility of hepatotoxicity. There may be possibility of prolonged absorption of APAP, and a measurable amount of APAP is still present after the completion of IV NAC therapy. NAC therapy should be stopped if there is no APAP and if no improvement is observed. Anaphylactoid reactions are reported while treating with IV NAC; these reactions are very mild and are treatable. Hazardous reactions do not occur commonly. In case of children, IV NAC is tolerated very well. Dose or formulation of NAC should modified before administering NAC therapy in patients who have weight less than 40 kg, so that excessive fluid administrated can be prevented. Many recent investigations also support that the patient related factors also affect the therapy. The patient's clinical status and the data obtained in laboratory works should be considered for deciding the duration of treatment.

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