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Multidrug toxicity in a newborn: A case report.

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Abstract

Neonates are more vulnerable to the effects of medication errors. Herein we will report an infant who was given adult doses of sefdinir/clavulanic acid, paracetamol, iron III hydroxide and bemiparin sodium accidentally by his parents for 3 days and admitted to the hospital with severe acute kidney injury, and focal convulsions. Herein, the kidney functions were affected more greatly by multidrug toxicity than hepatic functions and severe metabolic acidosis was one of the main problems in this case. By this way, we aimed to take attention to the multidrug toxicities in neonates.

Keywords: Kidney, Hospital, Toxicity.

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Introduction

Unfortunately, neonates are mostly vulnerable to the effects of medication errors [1]. Adverse drug reactions and potential drug-drug interactions may cause severe life-threatening concerns in newborns and infants [2]. Physicians must be careful when prescribing medications for infants since the data is limited especially in drug interactions. On the other hand, potential drug toxicities due to the overdoses of medications accidentally given to the infants are also important. In that regard, both the parents and caregivers of the infants should also be very careful.

Inappropriate formulations, poly-pharmacy, immature organ functions and underlying illnesses were defined as the main risk factors for adverse drug reactions in neonates and infants [3]. Kurian et al. [4] defined that; infants, males and those receiving ≥ 4 number of medications were at risk of developing adverse drug reactions.

Herein we will report an infant who was given adult doses of sefdinir/clavulanic acid, Paracetamol, iron III hydroxide and bemiparin sodium accidentally by his parents for 3 days and admitted to the hospital with severe acute kidney injury and focal convulsions. By this way, we aimed to take attention to the multidrug toxicities in neonates.

Case Report

A 4 day old male was referred to our emergency department from a community hospital with the diagnosis of multidrug toxicity. The patient was born at 41 weeks' of gestation after an uneventful vaginal delivery to a gravida 7 mother. The pregnancy was also uneventful. The parents were non-consanguineous.

It was learnt from his parents that, he had been given sefdinir/clavulanic acid 300/125 mg 2 × 1 po, Paracetamol 500 mg 2 × 1 po, iron III hydroxide 1 × 1 po and bemiparin sodium 3500 iu sc for 3 days. Although those drugs were prescribed for his mother, it was misinterpreted by the parents, in that they supposed the medications were for him. Since his general condition got worse, they brought the newborn back to the hospital after 3 days and the error was discovered.

The newborn was 3250 g at admission. His vital signs were as follows; heart rate was 135/min, blood pressure was 78/56 mm Hg and body temperature was 37.3ºC. His physical examination revealed that, he was lethargic and his spontaneous motor functions were weakened. At emergency department, he had a focal convulsion on left arm that was treated with midazolam and phenobarbiturate. He was diagnosed with acute kidney injury and neonatal convulsions due to multidrug toxicity. The neonate was put in a pre-heated incubator. Gastric lavage was performed, umbilical catheter was inserted and blood was drawn for the analyses. He was started to be hydrated with 10% dextrose as 120 cc/kg iv; 1 mg vitamin K iv was applied and bicarbonate treatment was started for the patient since he was having severe metabolic acidosis. He was monitored and blood exchange was performed with 1 unit complete blood on the first day of hospitalization. During exchange, his respiration became shallow and he was intubated. A standard intravenous N-acetylcysteine protocol was started with 150 mg/kg of N-acetylcysteine mixed in 12

mL of 5% dextrose (3 ml/kg) and infused over 60 min, followed by 50 mg/kg of N-acetylcysteine mixed in 40 mL of 5% dextrose (10 ml/kg) and infused over 4 h, then 100 mg/kg of N-acetylcysteine in 80 mL of 5% dextrose (20 ml/kg) infused over 16 h. The acetaminophen blood concentration was determined as 215 μmol/L (therapeutic range: 66-199). The laboratory data at admission and during follow-up are summarized in Tables 1-3.

The regional poison control center was consulted. Given that the patient had received 4 different drugs at toxic doses, they also advised close follow-up of the newborn in Neonatal Intensive Care Unit (NICU). Desferrioxamine infusion (5 mg/kg, 4 h infusion) was also started for the iron toxicity. The patient was monitored in NICU. He was followed as intubated for 19 days and during this time period; his general condition was not good. After recovery of the renal functions, potassium replacement (1 mEq/kg) was started. His blood glucose levels and arterial blood gas analyses were closely followed. N-acetylcysteine treatment was stopped on the 4th day of admission since his acetaminophen blood concentration was determined as <3 μmol/L and on the same day his enteral feeding was started by the aid of oro-gastric tube. Cranial ultrasound performed on the 3rd day revealed widespread, mild increase on echogenity. Any focal or generalized convulsions were not noted during follow-up. Prophylactic Sulperazon treatment was started on the 6th day of his admission due to the prolonged intubation. On the 19th day of his hospitalization, he was extubated. During follow-up any convulsions were not determined and Electroencephalography (EEG) and cranial magnetic resonance imaging performed on the 20th day were also normal. We could not perform EEG before since he was intubated.

The patient was discharged as healthy after 24 days of hospitalization in NICU. He was clinically well without any sequel of the accidental multidrug overdoses during discharge.

Table 1. *Hematological parameters and blood gas analyses results*

Hemoglobin-1st day (g/dl) (N:15-24.6)	13.4
Hemoglobin-3rd day (g/dl)	13.1
Hemoglobin-5th day (g/dl)	11.5
Iron-1st day (μg/dL) (N:100-250)	131.88
Ferritin- 3rd day (N:20-200)	541.8
Ferritin-5th day	119.2
Blood gas analysis on admission	
pH	7.18
pO_2	56
pCo_2	54
Base excess	-14
HCO_3	9
Blood gas analysis-2nd day	
pH	7.33
pO_2	56
pCo_2	48
Base excess	5
HCO_3	21

Table 2. *Liver and renal function tests*

Creatinine-1st day (mg/dl) (N:0-0.4)	4.58
Creatinine-2nd day (mg/dl)	3.15
Creatinine-3rd day (mg/dl)	1.24
Creatinine-5th day (mg/dl)	0.70
Uric acid-1st day (mg/dl) (N:2-5.8)	16.4
Uric acid-3rd day (mg/dl)	5.6
Uric acid-5th day (mg/dl)	2.5
BUN-1st day (mg/dl) (N:10-50)	106.6
BUN-3rd day (mg/dl)	61.2
BUN-5th day (mg/dl)	17.3
AST-1st day (U/L) (N: 15-60)	36.1
AST-3rd day(U/L)	17.1
ALT-1st day (U/L) (N: 10-60)	25.6
ALT-3rd day(U/L)	7.6
GGT-1st day (U/L) (N: 10-45)	22.4
LDH-1st day (U/L) (N: 0- 1732)	1325
Albumin 1st day (g/dl) (N:3.5-5.5)	4.2
Total protein1st day (g/dl) (N:6-8.3)	6.9
PTT 1st day (sec) (N: 9.5-13.5)	24.7
PTT 2nd day (sec)	15.4
APTT 1st day (sec) (N: 21.0-34.0)	41.9
APTT 2nd day	32.2

N: Normal; BUN: Blood Urea Nitrogen; ALT: Alanine Amino Transferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; PTT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time

Discussion

Neonates, owing to their low weights, are more vulnerable for drug reactions and toxicities. Moreover, sufficient pharmacodynamic studies in neonates are also not present about many medications. Herein we reported a multi-drug toxicity causing acute kidney injury and convulsions in a newborn that was treated successfully with close follow-up in NICU.

Parents or the caregivers should be very careful about the medications of new-borns. Size, maturation and organ functions are the main variables determining drug responses in neonates [5]. It is also important to emphasize that, in mixture toxicities, single compound toxicity data may not be sufficient to predict the overall harmfulness [6]. In that regard, mixture toxicities are more dangerous requiring additional attention. Herein, we have reported a 4 days old infant who was given sefdinir/clavulanic acid, Paracetamol, iron III hydroxide and bemiparin sodium at adult doses. Although he was diagnosed with acute kidney injury and severe metabolic acidosis at admission to the hospital, he was successfully treated without any sequel in NICU.

Severity of underlying disease and the drug doses are also important in clinical practice during the drug toxicities.

Table 3. *Other biochemical parameters including electrolyte levels*

Sodium-1st day (mEq/L) (N:131-144)	154
Sodium-2nd day (mEq/L)	152
Sodium-4th day (mEq/L)	145
Potassium-1st day (mEq/L) (N:3.2-5)	5.29
Potassium-2nd day (mEq/L)	2.82
Potassium-4th day (mEq/L)	2.27
Potassium-6th day (mEq/L)	2.02
Chloride-1st day (mEq/L) (N:97-108)	111
Chloride-2nd day (mEq/L)	107.7
Chloride-4th day (mEq/L)	106.5
Calcium-1st day (mg/dl) (N:8-10.6)	7.71
Calcium-3rd day (mg/dl)	7.54
Calcium-5th day (mg/dl)	9.48
Phosphorus-1st day (mg/dl) (N:3.9-7.7)	8.44
Phosphorus-2nd day (mg/dl)	6.15
Procalcitonin-1st day (ng/ml) (N:0-0.50)	9.09
Procalcitonin-2nd day (ng/ml)	0.05
CRP-1st day (mg/L) (N:0-5)	1.98
CK-1s day (U/L) (N:0-295)	1111
CK-2nd day (U/L)	501
CK-3rd day (U/L)	208

CK: Creatinine Kinase; CRP: C Reactive Protein

Although there was not an underlying disease in our case, the doses of the medications were very high.

Drug induced nephrotoxicity is one of the main concerns in neonates since the maturation of the kidneys may be incomplete and various therapeutic agents may have a potential for inducing renal tissue injury [7]. Acute kidney injury is defined as an abrupt decline in renal functions due to severe tissue damages along the nephron. In this reported case, acute kidney injury was one of the main problems at admission that was treated successfully. Glanzman et al. [8] studied about the nephrotoxic medication exposure in a pediatric intensive care unit and reported that patients treated with paracetamol had a higher risk of developing acute kidney injury as well as the children treated with metamizole, morphine and tropisetron.

The severe hepatotoxicity induced by paracetamol, is not common in the neonatal period, but this drug is mainly associated with liver failure in older children [9]. Bucaretchi et al. [10] defined an acute liver failure in a term neonate associated with repeated paracetamol administrations. Similarly Walls et al. [11] also reported a case of oral acetaminophen toxicity in a term new-born displayed with hepatic failure and encephalopathy. In our case, the infant was treated about 10 times more than the upper limit of paracetamol dose for 3 days. Moreover, there were high levels of ferritin, uric acid and LD but interestingly we did not determine any findings associated with acute liver failure in this case and his liver function tests including transaminases, total bilirubin and prothrombin time were all normal. However, since N-acetylcysteine is the antidote in the treatment of acetaminophen poisoning, N-acetylcysteine treatment was also given. On the other hand, to the best of our knowledge, paravetamol associated acute renal failure was not reported before in neonates.

Cephalosporins are one of the most commonly prescribed antibiotic groups in infants. Arnold et al. [12] reported that, seizure was the most commonly observed clinical adverse event in infants treated with a cephalosporin group antibiotic in first 120 days of their life, with an incidence of 3-4%. In our patient, focal convulsions determined at admission may also be associated with the toxicity of Sefdinir that is a third generation cephalosporin. During follow-ups at NICU there was not any convulsions reported. However, focal seizures defined at admission may also be associated with other medications given to him [13]. On the other hand, cephalosporins are water soluble and are primarily eliminated with the urine [14]. Renal tubular necrosis was reported in adults associated with the cephalosporin toxicity [15]. Acute renal failure in our patient may also be associated with the high doses of third generation cephalosporin administrations.

Conclusion

In this case report we aimed to highlight the importance of multidrug toxicities that may be fatal in neonates. Herein, interestingly the kidney functions were affected more greatly by multidrug toxicity than hepatic functions and severe metabolic acidosis was one of the main problems in this case. If diagnosed promptly and treated appropriately, newborns would recover without any sequel. The type, and dose of medications as well as the underlying diseases and maturation level of infants are important in drug toxicities but in multi-drug toxicities the effects may be unpredictable.

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