Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 02, February, 2018, Pages 53 - 58, Available @ www.damaacademia.com

Ceftriaxone and DHF Induced Hepatocellular Enzyme Elevation in Pediatric: Focus on Management

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Abstract
There is no spesific treatment for patient with hepatocellular enzyme elevation caused by dengue and/ or cefriaxone. We report a child with transaminitis caused by dengue and/ or cefriaxone. A 9-months-old girl was diagnosed dengue haemorrhagic fever grade III with transaminitis. After administration of intravenous N-acetylcysteine and Ursodeoxycholic acid, a rapid decrease in liver transaminase was observed followed by clinical improvement.

***Keyword**: N-acetylcysteine, ursodeoxycholic, dengue, liver injury, paediatric*

I. INTRODUCTION

Hepatocellular damage releases alanine transaminase (ALT) and aspartate transaminase (AST) into the bloodstream. Many factor can induced hepatocellular damage include medication and dengue virus infection (Robert C & Hustead, 2011). Dengue infection is usually associated with mild to moderate elevations of ALT and AST (Mahmuduzzaman et al, 2011; Roy A et al., 2013). The degree of elevated is associated with the severity of the illness (de Souza LJ et al., 2007; Ahmed A et al., 2014). Mechanisms of liver injury in dengue may be due to direct cytopathic effects of virus or immune response of host, and/ or hypoxia caused by hypotension or localized vascular leakage inside the liver (Mohan et al, 2017). Drugs are also significant cause of liver injury. Ceftriaxone is a commonly used antibiotic and has been associated with reversible biliary sludge, pseudolithiasis and cholestasis (Khurram, et al., 2015). The incidence may be higher in children than adults and is associated with higher doses and longer courses of treatment and possibly with fasting or dehydration. Most cases occur with minimal or no symptoms (Moseley RH, 2013). The therapy for Liver injury can be classified in two; medical and surgical treatment (ex: transplantation). The aim of medical treatment are repairing liver physiological function and giving the liver time to recover. The medical treatment are including plasmafaresis, prostaglandin E1, dan N-acetylcysteine (NAC) (Cochran et al, 2007; Abeysekera et al 2012). Some case reports about hepatocellular enzyme elevation had been published, but lack of them occur in Indonesian Population. The aim of this study is to report hepatic enzyme elevation that suspected induced by dengue infection and/ or ceftriaxone in pediatric and the management of theraphy in this patient.

II. CASE REPORT

A previously 9-months-old girl was admitted to Aisyiyah Bojonegoro with a 5-day history of fever, nausea, vomited when drinking milk, and 2-day diarrhoea 5 times a day. Investigations at the emergency room revealed haematocrit of 42% and thrombocyt of 172.000. A diagnosis of dengue haemorrhagic fever grade III with transaminitis was made. She was resuscitated with 100 ml of Asering. She was started on therapy with zinc 10 mg daily; probiotic two times daily and paracetamol 100 mg three times daily. On day 6 she was started on therapy with ceftriaxone 200 mg two times daily for 4 days. Upon admission, liver function test revealed transaminitis—aspartate transaminase (AST) 352 U/l and alanine transaminase (ALT) 270 U/l. Laboratory investigations showed decreased of albumin of 2.9 and worsening transaminitis (AST 3320 U/l and ALT 5570 U/l) on day 10. On day 10 intravenous NAC and Oral Ursodeoxycholic acid was given. Intravenous NAC was started at 100 mg twice daily for 3 days and continued 200 mg twice daily for 4 days. Oral Ursodeoxycholic acid was started at 75 mg three times daily for 2 days and continued 20 mg three times daily for 5 day. A marked improvement in liver enzymes was noted: AST dropped to 1050 U/l and ALT 350 U/l after 3 days; AST to 575 U/l and ALT to 173 U/l, respectively, after 5 days (Fig. 1).

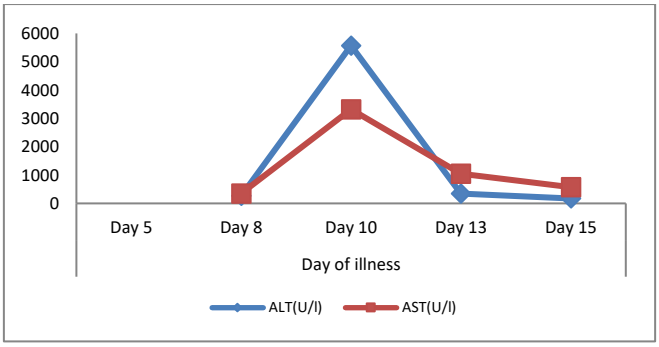

Fig.1. Trend of liver transaminase in the relation to day of illness

Table 1. Relevant Clinical features investigation to day of illness

	Day of illness										
	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
Heart rate (x/minutes)	148	100	110	114	86	86	98	100	98	100	98
Respiration Rate (x/minutes)	40	33.8	40	33.4	37.8	32.5	36	36	37	36	36

Table 2. Relevant laboratory investigations in relation to day of illness

	Day of illness				
	Day 5	Day 8	Day 10	Day 13	Day 15
Hb (g/l)	13.2	11.2	9.7	8.8	
WBC ($X10^9$)	8.500	3.900	7.400	9.500	
Hct ($X10^9$)	42	36	32	27	
Thrombocyt	172.000	29.000	53.000	110.000	
Eritrocyt	5.22	4.47	3.96	3,33	
Diff count	-/-/1/14/82/3	-/-/23/66/1	-/-/1/24/73/2	-/-/1/25/66/8	
LED		40			
Albumin			2.9	2.7	3.4
ALT(U/l)		270	5.570	350	173
AST(U/l)		352	3.320	1.050	575

NAC and UDCA was given for a total period of 5 days from Days 10–15 of illness. WBC, White Blood Cell count; Hb, Haemoglobin; Hct, Haematocrit.

III. DISCUSSION

Abnormal liver enzyme levels may signal liver damage or alteration in bile flow. The timing of liver enzyme abnormalities in relation to the age of patient, comorbid conditions and ingestion of medications provides valuable information (Giannini, E. G, et al., 2005). The course of all comorbid conditions must be fully explored, along with a detailed list of drugs being taken by patient and date they were started in relation to the onset of enzyme alterations or of symptoms of disease. Full assessment of enzyme abnormalities involves evaluation of (1) the predominant patters of enzyme alteration (hepatocellular vs cholestatic), (2) the magnitude of enzyme alteration in the case of aminotransferase (<5 times, 5-10 times, >10 times the upper reference limit), (3) the rate of change, and (4) the nature of the course of alteration (e. g., mild fluctuation or progressive increase (Lee, 2003).

Multiple mechanisms can cause hepatocellular enzyme elevation such as hypoxia, respiratory disorders, circulation disorders, drugs, trauma and infection (Soleimanpour, et al., 2015). In this report, we focus on hepatocellular enzyme elevation due to dengue virus infection and drugs (ceftriaxone).

Hepatic involvement in dengue infection is often demonstrated by hepatomegaly and mild to moderate increase in transaminase levels. High mortality has been reported in children with dengue infection with acute liver cell failure (Povoorawan, et al., 2006; Kumar, et l., 2008). Dengue virus infection is an important health issue in many Southeast Asian countries, including Indonesia. Dengue virus is a type of flavivirus transmitted by mosquitoes of

the Stegomyia family (Halstead, 2016). The symptoms of infection by this virus range from asymptomatic or mild symptomatic dengue fever (DF) to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Mishra G et al., 2015). Dengue infection is usually associated with mild to moderate elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Mahmuduzzaman et al, 2011; Roy A et al., 2013). Hepatic involvement in DF is common and it is usually mild with transaminases of less than 5-foldincrease (Nguyen, 1997). Previous studies have reported dengue associated liver injury appears to peak around day 6 and 7. Therefore, liver function tests done at earlier dates might not reflect the extent of liver involvement in acute infection (Fernando et al, 2016).

Cephalosporin include ceftriaxone can cause inflammation of portal areas with bile duct injury (cholangitis) (Friedman, 2016). Although a definitive diagnosis of DILI due to ceftriaxone requires a tissue sample for analysis, a liver biopsy was not pursued. In our patient humanitarian grounds liver biopsy was not done in any children to confirm the diagnosis.

Ceftriaxone's contribution to this patient was scored as a possible adverse drug reaction (ADR) on the naranjo nomogram (Table 3), a validated method for estimating the probability of ADR. In this case there was no re-challenge, thus the patient's ceftriaxone could be related to the abnormal liver enzyme levels.

Table 3. The Naranjo adverse drug reaction (ADR) probability scale12 for this case: a score >9 indicates definite ADR; 5–8 indicates probable ADR; 1–4 indicates possible ADR; and 0 indicates doubtful ADR

NO		Yes	No	Do not Know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
6	Did the reaction appear when a placebo was given?	-1	+1	0	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8	Was the reaction more severe when the dose was increased, or less severe when dose decreased?	+1	0	0	+1
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0

10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1

Management of patients with dengue with acute liver failure (ALF) in children include supportive therapy for hypoglycaemia, coagulopathy, immune deficiencies, encephalopathy and cerebral oedema (Yong, 2006). The patient's drug list must be reviewed daily, and hepatotoxic drugs should be discontinued or required hepatic dosage adjustment to reduce further liver injury. Paracetamol is commonly used as an antipyretic drug in dengue patients. In the critically ill with marked elevations in liver aminotransferases, paracetamol-induced hepatotoxicity should be considered and excluded. Liver function generally normalizes during the recovery phase, and the patient should expect full hepatic recovery with no long-term effects to the liver (Lee et al, 2016). Current treatments of acute liver failure in dengue infection include (Intravenous N-acetylcysteine) NAC, prostaglandin E1 and plasmapheresis and extracorporeal systems like molecular adsorbent recirculating system (MARS) (Yong, 2006).

The rationale for N-acetylcysteine (NAC) use as an adjunctive therapy is its ability to restore hepatocellular glutathione, and its action as a free radical scavenger. In addition, NAC may improve antioxidant defense (Senanayake *et al*, 2013; Habaragamuwa and Dissanayaka, 2014). There is limited data regarding the use NAC in non-acetaminophen-induce liver injury. Table 4 show some publicatian regarding of treatment with N-acetylcysteine (NAC) in patient with elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Table 4. Summary of The outcomes of treatment with N-acetylcysteine (NAC) in patient with elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Studies	Dose	Case report	LFT – presentations	Outcome
Habaragamuwa *et al*, 2014	100 mg/kg/day intravenously for 5 day	54-year female	Acute liver failure; AST 16,261 U/l; ALT 4,545 U/l, INR 1.7, TB 6 mg/dl	Survive with normal liver tests in 2 weeks
Senanayake, 2013	100 mg/kg intravenously over 24 hr and continued up to 72 hours	*n*=7 cases; ages 6 months-12 yrs	hepatomegaly, impaired level of consciousness, serum alanine transaminase levels (ALT) >500 IU/l and prothrombin time / INR >1.5.	Successful outcome
Lim and Lee, 2012	100 mg/kg/day	6-year-old boy	Acute liver failure	Successful outcome
Abeysekera *et al*, 2012	LD: 150 mg/kgBB in 100 ml NS over1 hr Dose 2: 50 mg/kgBB in 200 ml NS over 4 hr, Dose 3: 150 mg/kgBB in 500 ml over 24 hr in 3 days.	52-year	AST 1857 IU/I; ALT 90,4	Successful outcome
Kumarasena *et al*, 2010		*n*=7 cases; ages 6 months-12 yrs	Acute liver failure	Successful outcome

Ursodeoxycholic acid has hepatoprotector effects, which are thought to be principally to display of more hydrophobic and toxic bile acid (e.g lithocholic acid) that accumulated in the setting of cholestasis (Kowdley KV, 2000). Ceftriaxone induced hepatotoxicity has been associated with biliary sludge and cholestasis. Ursodeoxycholic acid was given to treat liver injury, in this case we suspected that ceftriaxone is one of the cause of the liver injury. Evidance base of UDCA in patient with elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) show in table 5.

Table 5. Summary of The outcomes of treatment with Ursodeoxycholic acid (UDCA) in patient with elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Studies	Dose	Case report	LFT-presentations	Outcome
Asgarshirazi, M. *et al.* 2015	250 mg in dose of 10-15 mg/kg/day once day	54 children aged between 4m0-14 year	Pretreatment transaninases : ALT 115,782 µl, AST 88,434 µl, gamma GT 122.521 µl After one month : ALT 65.173 µl, AST 88.434 µl, gamma GT 57.782 µl	ALT and AST decreased in patients in UDCA groups in one month intervention.
Ranucci G, *et al*. 2008	20mg/kg daily	Age 17 month	Before treatment ALT 2147 µl. after 4 month score for AIH (autoimmune hepatitis) was negative. After 6 months therapy ALT 23 µl	ALT decreased in patients in UDCA in after 6 mounth
Willot, S. *et al*. 2008	25 mg/kg per day (range 20-36) mg/kg day	3mo-7year	-	Successful outcome

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