ORIGINAL ARTICLE

USEFULNESS OF N-ACETYLCYSTEINE AS HEPATOPROTECTIVE AGENT IN CHILDREN INFECTED BY HEPATITIS A VIRUS

María de los Ángeles Durazo-Arvizu, Karina Azpeitia-Cruz*, Roberto Dórame Castillo*, Manuel Alberto Cano-Rangel*, Norberto Sotelo-Cruz***

Abstract

Introduction: All forms of viral hepatitis are acute and/or chronic and transmissible. In less developed countries, they are considered a public health problem. The objective of this study was to examine the clinical effects of the oral administration of N-acetylcysteine (NAC) as hepatoprotective agent in pediatric patients infected with hepatitis A virus. **Materials and Methods:** Fifty patients were studied. Group A (20 children) received N-acetylcysteine (50mg/kg) orally for 7 days. Group B (30 children) received no medication. The variables studied were: age, hepatitis-related signs and symptoms, fever, malaise, anorexia, nausea, vomiting, abdominal pain, jaundice, choluria, acholia, and undesirable effects of the drug. Laboratory tests were performed at baseline and 8 days later: complete blood count (CBC), glucose, total protein, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), bilirubin, urinalysis, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The results were analyzed using parametric and non-parametric statistical tests. **Results:** In group A, the mean age was 8 years (65% male); in group B, the mean age was 8.3 years (56.6% male). There were no differences in clinical or laboratory manifestations. After 7 days of therapy, ALT (324 ±250.9 vs. 720.2 ± 582 IU/L) and AST (134.2 ± 108 vs. 502.4 ± 518.3) were much lower in the patients who received NAC as compared to the controls ($p<0.006$ and $p<0.003$ respectively). No adverse effects were noted in the treated cases. **Conclusion:** The oral administration of NAC helps to significantly reduce liver enzymes and is safe.

Keywords: Hepatitis A, N-acetylcysteine, cytoprotection, aminotransferases, acute liver failure

Introduction

All forms of viral hepatitis are transmissible, acute and/or chronic diseases; they have become particularly important worldwide due to their significant morbidity and mortality, and are considered a public health problem. (1,2) Hepatitis A virus infection (HAV) follows the fecal-oral route from person to person; risk factors include ingesting food or drinks contaminated by feces containing HAV, unhealthy practices such as not washing hands properly after using the bathroom, and sex acts involving both oral and anal contact. HAV has a high prevalence in some countries, particularly in the South Asia or Latin America. (1-5) Some people are highly exposed due to their work activity: health workers, food handlers, people involved in wastewater control, military personnel, nursery employees and childcare centers, as well as the children attending these places. (1,3,4) In 2005, HAV infection caused the death of 34,000 people around the world. Between 2012 – 2013, in Mexico, it affected 39,774 patients, 75% of which were children. The mortality associated with this disease is 1% (1-3); furthermore 1% of those infected will develop acute liver failure (ALF). Mortality rate of ALF is 65-90%. Between 15 and 26% of the subjects accepted in liver transplant centers had developed acute liver failure caused by HAV. (6-16)

When an HAV infection is diagnosed, it usually does not receive any treatment and is allowed to evolve naturally; it is thus necessary to offer hepatoprotective agent that prevent a child with this condition from evolving to ALF. In this regard, uncontrolled observations of patients of an outpatient clinic in Sonora showed that the oral administration of N-acetylcysteine (NAC) induced a decrease of aminotransferases in a shorter time than the natural course of the disease. NAC has shown benefit in previous studies. (7,11-13). This work had the aim of evaluating the clinical usefulness of this drug in children with hepatitis A.

Methods & Materials

This was a longitudinal and comparative study of 50 patients (aged from 1 to 17 years), of a public pediatric hospital in northwestern Mexico that attended the outpatient clinic or the hospital emergency room. The study was approved by the hospital ethics committee. The clinical signs of patients with suspected infection of HAV (clinical or prodromal, evidence or association with a family member with HAV infection or with an outbreak of HAV infection) were recorded and the following tests were requested: complete blood count (CBC), urinalysis, bilirubin, glucose, total proteins, prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), as well as serologic tests for hepatitis viruses A, B and C. The clinical signs were obtained by systematic sampling, prior authorization and informed consent of parents and adolescents. Fifty patients with confirmed diagnosis by clinical features, laboratory tests and by serological, antibodies IgM against hepatitis A Virus (IgM-HAV) were divided randomly into two groups: 20 patients in group A received N-acetylcysteine (50 mg/kg) orally in three doses for 7 days and 30 patients in group B did not receive NAC. The greater number of controls was with the purpose to have greater statistical solidity.In previous studies, NAC has been administered in doses ranging from 15 to 100 mg/kg/day. (9,12) For the purpose of the study, we decided to use an average dose of 50 mg/kg/day. Patients with signs of acute liver failure (ALF) (10,12) and those who declined to participate in the study were excluded from the study. The collection of data was performed using a data-collection instrument designed for this purpose. Laboratory tests were performed on the eighth day after starting treatment; clinical signs and manifestations associated with tolerance and effects of the medication were also recorded at this time.

Statistical Analysis: The data obtained were

subjected to the following statistical tests: Chi square test to compare proportions between groups; Student's T-test to compare means between groups; variance analysis, and correlation coefficients to analyses the association between variables.

Results: The baseline clinical and laboratory characteristics in both the groups are depicted in Table 1. After 7 days of therapy, ALT and AST were much lower in the patients who received NAC as compared to the controls ($p<0.006$ and $p<0.003$ respectively). (Table 2). No adverse effects were noted in the treated cases.

Table 1. Signs and symptoms in patients with hepatitis A in both the groups

CHARACTERISTICS	Group A (N=20) (%)	Group B (N = 30) (%)	P value
Age (years)	8 ± 4.2	8.3 ± 3.7	0.76
Gender			
Female	7 (35)	13 (43.3)	0.38
Male	13 (65)	17 (56.66)	
Clinical Features			
Asthenia	9 (45)	10 (33.33)	0.2
Hepatomegaly	13 (65)	18 (60)	0.47
Malaise	11 (55)	8 (26.66)	0.042
Nausea	13 (65)	22 (73.33)	0.42
Vomiting	4 (29)	8 (26.66)	0.37
Myalgia	3 (15)	0	0.05
Diarrhea	3 (15)	5 (16.66)	0.59
Pruritus	0	0	-
Jaundice	18 (90)	29 (96.66)	0.34
Acholia	4 (29)	5 (16.66)	0.52
Choluria	10 (50)	11 (36.66)	0.26
Hepatomegaly	4 (29)	4 (13.33)	0.4
Splenomegaly	2 (10)	0	0.15
Laboratory Features			
Prothrombin time (sec)	15.8 ± 3.1	15.2 ± 2.1	0.42
Blood glucose (mg/dl)	85 ± 13	88.9 ± 15.4	0.3
Direct Bilirubin (mg/d1)	4.7 ± 3.2	6.4 ± 4.7	0.15
ALT (IU/L)	1522.4 ± 1009.3	1527.4 ± 1217	0.98
AST(IU/L)	1459.6 ± 829.8	1286.7 ± 897.9	0.58
INR	1.2 ± 0.3	1.2 ± 0.2	0.88
LDH	986.9 ± 817	813.5 ± 343.5	0.3
Albumin (g/dl)	4 ± 0.4	3.8 ± 0.4	0.3

Note: INR - International Normalized Ratio, AST - aspartate aminotransferase, ALT - alanine aminotransferase, LDH- lactate dehydrogenase

Table 2: Effects of N-acetylcysteine in children with Hepatitis A after 8 days of treatment

	Group A (n= 20)	Group B (n= 30)	P value
Prothrombin time (sec)	13.9 ± 1.3	14.1 ± 1.0	0.68
Glucose (mg/dl)	91 ± 10	92.3 ± 8.5	0.61
Direct bilirubin (mg/dl)	2.6 ± 2.1	10 ± 3.1	0.19
ALT (IU/L)	324 ± 250.9	720.2 ± 582	0.006
AST (IU/L)	134.2 ± 108	502.4 ± 518.3	0.003
INR	1.1 ± 0.1	1.2 ± 0.6	0.28
Albumin (gm/dl)	4.1 ± 0.5	4 ± 0.5	0.82
LDH	476.7 ± 148.7	641.9 ± 372.7	0.06

Note: INR - International Normalized Ratio, AST - aspartate aminotransferase, ALT - alanine aminotransferase, LDH- lactate dehydrogenase

Discussion

One of the complications that may suddenly appear in patients with HAV infection is ALF. NAC, due to its cytoprotective effect has reduced the number of patients who develop this complication. (9,10,12) NAC is derived from cysteine, in which an acetyl group is attached to a nitrogen atom of the thiol type; it can be oxidized by a large variety of radicals and also serve as a nucleophile (electron donor pair). When thiolate anions that transport nitrogen dioxide in the form of toxic azide-type (N3) carbonate ions, or excess superoxide electrons, are added to thiols and hydroxyl radicals (OH), they efficiently reduce hydrogen atoms from sulphide radicals. In this reaction, thiolate anions also transport radicals that are not oxidants, such as hydrogen peroxide, nitrites, hypochlorous acid and excess thiols. (11,12,14-21) The intravenous use of NAC improves hepatic serological biomarkers in patients with liver failure of various kinds, especially in the early stages, inducing hemodynamic and oxygen transport improvements in cases of fulminant hepatic failure. (14)

NAC seems to help limit liver damage by accelerating the reduction in the levels of aminotransferases. (6-22) This agrees with the findings of this study regarding the decrease of the markers AST and ALT in less time than in patients receiving other drugs or no treatment. A study on the use of NAC in children aged 1 month and 16 years with fulminant liver failure secondary to HAV and who received treatment in a tertiary care center of a developing country, showed that the evolution of the patients was significantly associated with improvement in liver function tests. (22, 23)

In the present study, it was evident that the group that received NAC showed a significant reduction in liver enzymes. Furthermore, NAC is a safe drug that can be orally administered in pediatric ages, as was shown here; no patient showed any adverse effects such as nausea, stomatitis, vomiting, tinnitus, fever or hemoptysis, as has been suggested by the literature. (24) This will probably encourage other physicians to follow this line of work and recommend strong hepatoprotective alternatives to children living in countries with a high incidence of HAV infection but who do not benefit from a formal program of immunization against this disease. Using NAC could at least prevent the infection from developing into ALF. (5,16, 25-27)

Conclusion

The oral administration of NAC to patients with hepatitis A infection, showed no adverse effects and significantly reduced the levels of aminotransferases. This makes it possible to assume that NAC has an hepatoprotective effect on children with HAV infection.

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Conflict of Interest : None

References :

1. Mahteny SC, Kingeri Do JE, Hepatitis A. Amer fam Phys 2012; 86:1027-1034.
2. Dirección General de Epidemiologia. Boletín Epidemiológico. SSA, México 2012-2015. Available at URL: https://www.gob.mx/cms/uploads/attachment/file/50233/sem52.pdf. Accessed on 15th March 2018
3. Panduro A, Escobedo-Meléndez G, Fierro AN, Ruiz-Madrigal B, Zepeda –Carrillo AE, Román S. Epidemiologia de las hepatitis virales en México. Salud Pub Méx 2011; 53 Supl 1: S 37-44.
4. Valdespino JL, Ruíz-Gómez J, Olaiz-Fernández G, Arias-Toledo E, Conde-González CJ, Palma O, Sepulveda J, et al. Seroepidemiología de la hepatitis A en México. Sensor de inequidad social e indicador de políticas de vacunación. Salud Pub Méx 2007; 49 Supl 3: S 377–385.
5. Gil- Melgaco¸ J, Nóbrega- Morgado L, Almeida –Santiago M, Mendes de Oliveira J , Lewis-Ximenez LL, Hasselmannd B, Goncalvez-Cruz M, et al. A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that inducedby a natural infection. Vaccine 2015; 33: 3813–3820.
6. Ciocca M, Moreira- Silva SF, Alegria S, Galoppo MC, Ruttiman R, Porta G, Da Silveira TR, et al. Hepatitis A as an etiologic agent of acute liver failure in Latin America. Pediatr Infect Dis J 2007; 26: 711–715.
7. Lee WM, Hynan LS, Rossaro L, Fontana LJ, Stravitz RT, and Larson AM et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage nonacetaminophen acute liver failure. Gastroenterology 2009; 137: 856-864.
8. Squires RH, Schneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewiz MR, Dawan A, et al. Acute liver failure in children: The first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006; 148: 652-658.
9. Sotelo-Cruz N, Villalobos-García L, Sánchez-Santillán RM. Uso de N-acetilcisteina en la encefalopatía secundaria a hepatitis por virus A, en una adolescente. Rev Mex Pediatr 1997; 64: 257-261.
10. Sotelo N, Durazo MA, Ruiz- Villeda G. Correlation of neuropsychiatric signs with modified West- Haven scale on hepatic encephalopathy in children. Arch Neurocien 2010; 15:35-38.
11. Kortsalioudaki C, Taylor MR, Cheeseman P, Bansal S, Mieli VG, Dhawan A. Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. Liver Transpl. 2008; 14: 25–30.
12. Sotelo N, Durazo MA, Gonzalez A, Dhanakotti N. Early treatment with N-acetylcysteine in children with acute liver failure secondary to hepatitis A. Ann Hepatol 2009; 8:353–356.
13. Ben-Ari Z, Vakin H, Tur-Kaspa R. N-acetylcysteine in acute hepatic failure (no paracetamol induced). Hepatol Gastroenterol 2000; 47: 786-789.
14. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991; 324: 1852-1857.
15. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin N Am 2008; 92: 761-794.
16. Sotelo N. Pediatric viral hepatitis: avoiding liver failure. Pediatric Health 2010; 4: 613–622.
17. Bucuvalas J, Yazigi N, Squires RH. Acute liver failure in children. Clin Liver Dis 2006; 10: 149-168.
18. Macone A, Fontana M, Barba M, Botta B, Nardini M, Chirga F, Calcaterra A, et al. Antioxidant properties of amino acetylcysteine ketamine decarboxylase dimer: A review

. Int J Mol Sci 2011; 12: 3072-3084.
19. Squires H R, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez- Baez N, Dell Olio D, et al. Intravenous N-acetylcysteine in pediatric patients with non-acetaminophen acute liver failure. A placebo- controlled clinical trial. Hepatology 2013; 57:1442-1549.
20. Sales I, Dzierba AL, Smithburger PL, Rowe D, Kane-Gill SL. Use of acetylcysteine for non-acetaminophen-induced acute liver failure. Ann Hepatol 2013; 12:6-10.
21. Samuni Y, Goldstein S, Dean OM, Berk M. The chemistry and biological activities on N-Acetylcysteine. Biochim Biophys Act 2013; 1830:4117-4129.
22. Saleem AF, Abbas Q, Haque A. Use of N-Acetylcysteine in Children with Fulminant Hepatic Failure Caused by Acute Viral Hepatitis. J College Physicians Surgeons Pakistan 2015; 25: 354-358.
23. Parkas A, Asghar M, Haider N. Non-acetaminophen induced acute liver failure of viral etiology: treatment with and without N-acetylcysteine; comparing the length of hospital stay and survival status at the tertiary care hospital. Infect Dis J Pakistan 2016; 25:11-14.
24. Taketomo CK, Hodding JH, Kraus DM. Manual de prescripción pediátrica. 2011. 14 Ed. Intersistemas, México. p. 55- 58.
25. Guía de Práctica Clínica (SSA-214-09). Diagnóstico y Tratamiento de la hepatitis A. México Secretaría de salud; 2011. Available at URL: http://www.cenetec-difusion.com/CMGPC/SS-214-09/ER.pdf. Accessed on 15th March 2018
26. Franch MA, Redondo MP, Castro JM. La hepatitis como enfermedad emergente en pediatría. Boletín de la Sociedad de Pediatría de Asturias, Cantabria, Castilla y León, España 2002; 42: 151- 153.
27. Stuurman AL, Marano C, Bunge E, De Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines a systematic review. Hum Vaccin Immunother 2017;13: 724–736.

From: *Servicio de Infectología, del Hospital Infantil del Estado de Sonora, Hermosillo Sonora, México and **Departamento de Medicina y Ciencias de la Salud, Universidad de Sonora, Hermosillo, Sonora. México.

Address for Correspondence: Dr. Norberto Sotelo-Cruz, Professor Investigador Titular "B". Departamento de Medicina y Ciencias de la Salud de la Universidad de Sonora, Av. Luis Donaldo Colosio S/N entre Reforma y Francisco Q. Salazar, Colonia Centro, Hermosillo Sonora, México C.P.83000.

Email : nsotelo51@gmail.com
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