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Fulminant Hepatitis Managed with Pentoxifylline

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ABSTRACT

Introduction: Fulminant hepatitis is a severe clinical entity that has a prevalence of 10/1,000,000, and its mortality can reach 80% of registered cases. Its etiology is multifactorial and does not respect gender, age, or socioeconomic or cultural levels. Transcription factor NF-κB, oxidative stress, proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 and growth factors play a fundamental role in this pathology. Treatment-of-choice is liver transplantation; however, the latter is far from being the ideal solution due to its accessibility and cost. Thus, we use the Pentoxifylline inhibitor of NF-κB and inflammatory and oxidative processes.

Objective: To assess the response of patients with fulminant hepatitis using pentoxifylline.

Methods: The four pediatric cases, diagnosed and classified with fulminant hepatitis, presenting all indicators of poor prognosis according to the criteria of British Kings College. These patients received treatment with Pentoxifylline 200 mg every 12 h i.v. All patients received the following support treatment: fresh plasma; vitamin K; anti-ammonium measures; anti-cerebral edema (Mannitol); antimicrobials; ventilatory support; parenteral solutions, as well as parenteral and enteral nutrition (when they tolerated administration via the oral route).

Results: Presenting a favourable response to the on-average 2 weeks of treatment initiation, in relation to neurological, cognitive, and hemodynamic damage, with clinical and laboratory improvement, evaluating the patients discharged without presenting complications between days 8-10 days after leaving the Intensive Care Unit (ICU).

Conclusion: The results confirm previous observations and are encouraging for multicenter and randomized studies.

Keywords: Pentoxifylline; Hepatitis fulminant managed

INTRODUCTION

Fulminant hepatitis is the maximal expression of acute liver damage; it is accompanied by encephalopathy, cerebral edema, and in a large number of cases, multiple organ failure and death [1]. This entity is also characterized by having a diverse etiology and by affecting any age group, socioeconomic level, and geographic region [2]. Regarding its incidence, in the U.S., there are an estimated 2,000 new cases per year, a prevalence of 10/1,000,000 [3], with a mortality rate of 70-90% [4]. In a systematic review of studies between the years 2001 and 2011, it was reported that 2,891 patients underwent liver transplantation due to fulminant hepatitis, of which 1,948 were cases registered in the U.S. [5]. In Mexico, there are no precise statistics in this regard; however, at the Central Military Hospital of Mexico City, 11 cases were reported during a period of 10 years (1986-1995), with a mortality rate of 70%. The case studies are in agreement with those of other hospitals [6] confirming its high mortality rate. Also, multicenter studies have revealed that the main causes of fulminant hepatitis are as follows: a) viral origin of 2-32% of cases (hepatotoxic viruses such as A, B, C, D, and E, cytomegalovirus, herpes simplex, zoster varicella, and Epstein-Barr) [7-10]; b) biological origin by toxins from *Tinospora crispa* [11], and **c)** drug origin by overdose or iatrogenic. The most documented of include Paracetamol, Halothane, analgesics, sulfa, quinolones, statins, antihypertensives, antimicrobials, antimicrobials, and antiretrovirals [12,13]. Diverse origin, such as sepsis, neoplasms, eclampsia, circulatory problems, fatty liver, metabolic disorders, autoimmune diseases [14] and, in 25% of cases, other origins that could not be defined accurately. It is noteworthy that the causes of fulminant hepatitis do not exhibit the same incidence. Therefore, in the U.S. and Asia, the most frequent cause of fulminant hepatitis is the Hepatitis C Virus (HCV) and Hepatitis B virus

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(HBV) [9] while in Mexico some authors suspect the Hepatitis A Virus (HAV); in Africa, predominantly in pregnant women, the causative agent is the Hepatitis E Virus (HEV) [15]. On the other hand, medications in Europe predominate, with Paracetamol being the most frequently responsible for cases of fulminating hepatitis [13]. Clinically, fulminant hepatitis is diagnosed by the presence of jaundice, liver damage, and encephalopathy. According to the time of evolution, fulminant hepatitis can be classified as hyperacute (<8 days), acute (9-28 days), and subacute (>28 days); the latter entertains the worst prognosis [16]. On the other hand, during fulminant hepatitis, it has been observed that, as a consequence of the inflammatory process that the liver undergoes, Reactive Oxygen Species (ROS) and nitrogen derivatives are generated, as well as the release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, causing cellular damage [17-20].

The major problem in this clinical entity; they are the few options from the point of view of treatment, and liver transplantation is the only definitive treatment for fulminant hepatitis. However, this is far from being the ideal treatment due to the poor availability of organs, complications, and high costs [21,22]. Therefore, in patients with fulminant hepatic is necessary new treatments with greater accessibility and lower costs.

Pentoxifylline (PTX) 1,5-oxohexy l3,7-dimethyl-xanthine is a derivative of methylxanthines, with recognized hemorheological properties, providing stability and flexibility to the erythrocyte membrane, increasing the level of intracellular c-AMP [23], which has recently been described as an excellent antioxidant, with direct action on ROS and which indirectly inhibits nitric oxide synthetase [24-29]. This xanthine has already been employed in the clinic to inhibit liver damage in situations known to involve inflammation and oxidative stress such as caused by alcohol, radiotherapy, paracetamol or chemicals (carbon tetrachloride), and in septic endotoxemia [25]. PTX demonstrates other interesting effects at the cellular level. PTX it prevents the phosphorylation of the IκB complex in serine 32, making it impossible for transcription factor NF-κB to reach the nucleus. NF-κB induces the expression of various pro-inflammatory genes such as IL-1β, IL-6, and TNF-α as well as genes related to apoptosis inhibition. Properties that have even been utilized successfully in the area of Cancerology [26,30,31].

On the other hand, PTX has also been found to possess nephro and hepatoprotective effects. The effects of PTX may depend on its ability to inhibit TNF-α production, prevent the adherence of neutrophils to endothelial cells, and reduce inflammation by alleviating ROS generation by neutrophils [32].

Due to all of the aforementioned, and given that in fulminant hepatitis the participation of oxidative stress and the release of proinflammatory cytokines contribute significantly in the acute inflammatory process, increasing liver damage and cell death, we think that the antioxidant and anti-inflammatory properties of PTX could be useful in this condition. In this respect, our team has had success in two cases of fulminant hepatitis treated with PTX [33].

In the present work, we report four more cases of fulminant hepatitis that were successfully treated with PTX.

CLINICAL CASES AND METHODS

Four patients were diagnosed according to the following criteria: fulminant hepatic failure; cerebral edema; encephalopathy; jaundice; transaminasemia; prolonged International Normalized Ratio (INR), and multiple systemic damage on evaluating their severity according to the criteria of British College Hospital [34] (Table 1), presenting the hyperacute (etiology by ischemia-reperfusion) and subacute (Hepatitis by virus A) on the Gastroenterology Service of the Valentín Gómez Farías Hospital, Guadalajara, Jal. Mex. during the period from 2009 to 2018

Case 1

A 6-year-old female grade-school student arrives at the Pediatric Emergency Service due to presenting a clinical condition of hepatitis characterized by marked jaundice from the month prior to hospital admission. IgM antibodies against HAV were detected. On three or four occasions, she presented hematemesis 24 h before admission. At the initial physical examination, she was tired, irritable, confused, with changes in behaviour, responding only to painful stimuli, presented hepatomegaly 5 cm below the costal margin and hepatic pain. She was classified at that time with a score of 10 on the Glasgow scale, and fulminant hepatitis was diagnosed. The electroencephalogram reported acute encephalopathy; the computerized axial tomography discovered data of mild cerebral oedema. The study of cerebrospinal fluid was without important data. However, she presented hyperammonemia of 85 mmol/L (normal range=6.1 to 35 mmol/L) (Table 2). From the time of her admission, by means of a nasogastric tube, PTX treatment was initiated at a dose of 100 mg/12 h i.v. Treatment with anti-ammonium measures with L-ornithine-L-aspartate via nasogastric tube every 6 h, Vitamin K 2 mg/12 h i.v., Mannitol 0.4 mg/kg weight/12 h i.v., Sodium diphenylhydantoin 3 mg/kg weight/8 h i.v., Omeprazole 10 mg/12h i.v., Metronidazole 210 mg/8 h i.v., fresh plasma, parenteral solutions with 10% glucose, supplementary O_2 at a rate of 3 liters per min, and a hypercaloric diet based on fibers of vegetable origin. She remained in the Pediatric Intensive Care Unit (ICU) for 15 days, evolving favourably, with the decrease and disappearance of the clinical manifestations of cerebral oedema. Thus, she was transferred to the Pediatric Service, was administered the same treatment scheme, and became practically asymptomatic, tolerating the oral route. She left the hospital one week later, without sequelae, and continued with L-ornithine-L-aspartate 1.5 g every 12 h i.v., and PTX at a dose of 100 mg/12 h i.v., for 30 days.

Case 2

Child 6 years of age, is presenting in the Pediatric Emergency Service due to presenting jaundice of 1 month of evolution,

Table 1: Criteria for poor prognosis of fulminant hepatitis according to British Kings College.

Marker	Case 1	Case 2	Case 3	Case 4
Days of Evolution Intensive care unit/ Hospital stay (Total days)	15/23	14/24	15/25	14/25
Encephalopathy	Positive	Positive	Positive	Positive
Jaundice	Positive	Positive	Positive	Positive
Cerebral Oedema (Computerized axial tomography, and electroencephalography)	Positive	Positive	Positive	Positive
Prolonged Bleeding Time	Positive	Positive	Positive	Positive

Table 2: Laboratory tests on hospital admission and discharge of patients.

	Case 1			Case 2			Case 3			Case 4		
	ENTRY	EGRESS	Δ%	ENTRY	EGRESS	Δ%	ENTRY	EGRESS	Δ%	ENTRY	EGRESS	Δ%
TB (mg/dL)	24.7	8.6	-65%	4.3	0.6	-86%	13.51	2.97	-78%	5.42	3.98	-26%
DB (mg/dL)	25.2	6.3	-75%	2.1	0.3	-85%	10.47	2.54	-75%	3.91	3.40	-13%
AST (mg/dL)	1734	163	-90%	22.12	46	108%	3311	52	-98%	3296	43	-98%
ALT (mg/dL)	354	50	-85%	33.01	28	-15%	1307	181	-86%	3250	134	-95%
AF (mg/dL)	300	160	-46%	195	210	7.6%	182	100	-45%	101	108	7
LDH (mg/dL)	409	270	-33%	1024	200	-80%	8595	532	-93%	3890	389	90%
AMMO-NIUM (µmol/L)	85	15	-82%	85	22	-74%	80	26	-67%	165	30	-81%
INR	3.5	1.6	-54%	2.3	1.22	-46%	2.90	1.13	-61%	1.28	1.21	-54%

Abbreviations: Total Bilirubin (BT); Direct Bilirubin (DB); Aspartate Amino-transferase (AST); Alanine aminotransferase (ALT); Alkaline Phosphatase (AF); Lactic Dehydrogenase (LDH): International Normalized Ratio (INR). Δ%=percentage of increase or decrease in relation to determination of income.

epistaxis that recurs 3 times, with multiple ecchymoses throughout the body; hepatic pain, and hepatomegaly of 4 cm below the costal margin. Sodus data presented 24 h after admission, plus drowsiness and confusion, the reason for which he is directly admitted to the ICU, and IgM antibodies are detected against HAV. Physical examination revealed a poor general condition, generalized jaundice, abdominal distension, and ecchymosis, as well as collateral circulation, deviation of the gaze to the left, and bilateral positive Babinski sign, with the neurological classification of the patient with a Glasgow score of 12. He presented an important elevation in transaminases (Table 2). Computed tomography of the skull revealed data of cerebral oedema and the electroencephalogram contributed data of acute encephalopathy. He remained in the ICU for 14 days, where his management was practically similar to the previous patient, as follows: PTX 100 mg/12 h i.v.; anti-ammonium measures with L-ornithine-L-aspartate–L-aspartate 1.5 g via nasogastric tube every 6 h; Vitamin K 2 mg/12 h i.v.; Mannitol 0.4 mg/kg weight/12 h i.v.; Sodium diphenylhydantoin 3 mg/kg weight every 8 h i.v.; Omeprazole 10 mg/2 h i.v.; Metronidazole 210 mg/8 h i.v.; fresh plasma; parenteral solutions with glucose at 10%; ventilatory support and a hypocaloric diet based on fibres of vegetable origin through a nasogastric tube, in this case, 10 mg/12 h i.v. Later, the patient was moved from the ICU to the Pediatric Service with the same management, but the patients were now conscious and without data of encephalopathy, tolerating the oral route. Ten days later, he left the hospital without sequelae, with the same outpatient management as that of the previous case, that is, L-ornithine-L-aspartate-L-aspartate 1.5 g/12 h i.v. and PTX 100 mg/12 h i.v. for one month.

Case 3

Female, aged 4 years 8 months, with a history of right pulmonary systemic fistula and Tetralogy of Fallot. Her condition began after total correction of Tetralogy of Fallot, which lasted during 325 min of extracorporeal circulation and an aortic-clamping time of 269 min. The patient was discharged from an amine-dependent operating room, with ventilatory support and with data of systemic inflammatory response, presenting oliguria despite treatment with diuretic, hyperkalemia, hyperphosphatemia, persistent metabolic acidosis, and transaminasemia with a tendency to increase (Table 2). In addition, she presented cerebral edema data diagnosed by computed brain tomography. The patient was diagnosed with fulminant hepatitis by ischemia-reperfusion, and the following was added to the established treatment: Ranitidine 25 mg/12 h; PTX 200 mg/12 h i.v.; Sucralfate 10 mL/6 h via nasogastric tube and Metoclopramide 5 mg/12 h i.v. 12h i.v. Norepinephrine 0.05 mcg/kg/min, Ceftriaxone 50 mg/kg/12h i.v., Mannitol initial dose 1 g/kg whit maintenance dose 0.25 g/kg and reposition of bicarbonate according to the requirements. After 15 days of being treated in the ICU, the patient exhibited clinical and laboratory improvement of both renal and hepatic function, was extubated, and she was discharged from the ICU in order to be moved to the Pediatrics floor with an important decrease in transaminases (Table 2) and evident clinical improvement. The patients were discharged from the hospital 10 days after entering the Pediatrics ward.

Case 4

Female patient 11 years of age, diagnosed with Tetralogy of Fallot at birth and treated since then with acetylsalicylic acid. Antecedent of surgery 6 years previously to perform systemic pulmonary fistula, initiated with his liver disease after surgery for total correction of Tetralogy of Fallot, which had a duration of 339 min of extracorporeal circulation and an aortic-clamping time of 293 min. The patient left the operating room with amine-dependent cardiogenic shock, ventilatory support, with data on systemic inflammatory response, presenting oliguria despite treatment with diuretic, hyperkalemia, hyperphosphatemia, hypoglycemia, persistent metabolic acidosis, and transaminasemia with a tendency to increase (Table 2). In addition, she presented cerebral edema data diagnosed by computed brain tomography. Diagnosis of fulminant hepatitis by ischemia-reperfusion was made, and the following was added to the established treatment: Ranitidine 25 mg/12 h i.v.; PTX 200 mg/12 h i.v.; Sucralfate 15 mL via nasogastric tube every 6 h; Metoclopramide 10 mg/8 h i.v.; Norepinephrine 1 mcg/kg/min; Ceftriaxone 50 mg/kg/12 h i.v.; Mannitol initial dose 1 g/kg of weight with maintenance dose of 0.25 g/kg, and reposition of bicarbonate according to the requirements. After 14 days of treatment with intensive therapy, the patient was extubated and, due to clinical and laboratory improvement of both renal and hepatic function, she was sent from the ICU to the Pediatrics floor, with an important decrease in transaminases (Table 2) and evident clinical improvement. The patients were discharged 10 days after entering the Pediatric ward.

Statistical analysis

Measures of central tendency are described. In some cases, the Δ%, which represents the percentage of increase or decrease in relation to income values, was calculated, and significant changes were considered as ≥30%.

Ethical considerations

The parents signed and informed consent agreement and the protocol was approved by the Scientific and Ethical Committee, at the Hospital "Valentin Gómez Farías", ISSSTE with the number: ISSSTE/CEI-019-08.

RESULTS

In relation to the four patients, the majority of the clinical and paraclinical parameters demonstrated clear improvement (Table 2). In cases 1, 2, and 3, total bilirubin (TB) and direct bilirubin (DB) demonstrated a significant decrease between Δ%=-65 and 86%, while for case 4, the decrease only reached Δ%=-26 and -13 for TB and DB, respectively. It is likely that the percentage of decrease, in this latter case did not reach 30%, considered as significant, since their income values were not as high as compared with those of the other cases. In relation to Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), cases 1, 3, and 4 showed a significant decrease of Δ% of between Δ%=-85 and -95%; however, in case 2, a modification was not observed of AST (Δ%=108%). The behavior of Alkaline Phosphatase (AF) was found as more random, in that cases 1 and 3 showed a negative Δ%, reaching values of -45%, and cases 2 and 4 practically did not change in this regard. The Lactic Dehydrogenase (LDH) revealed more stable behavior. Four of the four studied cases exhibited an important decrease in their serum concentration in relation to the initial value of Δ%, that is, -33% for case 1 and a Δ%=-80 to -90% for the remaining three cases. On the other hand, in terms of the quantification of ammonium, the four cases demonstrated clear improvement (Δ%=-67% to -82%). The same behavior revealed the International Normalized Ratio (INR) achieved by the four patients, at discharge from the hospital, values very close to normal and with a Δ% between Δ%=-46% and Δ%=-61%. Taking all these results together, we can conclude that paraclinical improvement was observed in our study cases.

It should be noted that the four patients survived and had an average hospital stay of 3 weeks, a stay that is shorter than the required days for a liver transplant. This is important because it is known that patients with fulminant hepatitis with a clinical history of more than 10 days show a poor prognosis.

DISCUSSION

In this report, four cases were evaluated that met the clinical and laboratory criteria for the diagnosis of fulminant hepatic failure, with two in the subacute stage and two in the hyperacute stage, according to severity assigned by the British King's College classification [34]. As can be observed, the four patients had a favorable response to treatment, despite that the patients of this work presented grade III-IV encephalopathy and cerebral edema, considered manifestations of poor prognosis [35], and the mortality rate for fulminant hepatitis ranges from 70-90% [4,36], with the four patients being discharged asymptomatically, with minimal alterations in their laboratory tests and in an average time period in the ICU of 14-15 days. In this regard, it is noteworthy that the latter two cases of fulminant hepatitis treated in the Service prior to the use of PTX died, one with a diagnosis of hepatitis due to ischemia-reperfusion and the other, due to hepatitis A (data not shown).

The application of PTX was based on its antioxidant, anti-inflammatory, chemo- and radioprotective, antiangiogenic, and hemorheological properties [24,25,27,31,37]. It is important to note that PTX inhibits NF-κB, the transcription factor responsible for the generation of proinflammatory cytokines such as IL-1, IL-6, and TNF-α in leukocytes and the formation of ROS as the superoxide anion. In addition to decreasing the production of IL-2, IL-6, and IL-8 and C-reactive protein, it increases the production of Prostaglandins E2 (PGE2) and a blockade of adenosine receptors 1 and 2 [31]. Therefore, it is possible to consider that the multiple effects of PTX, and not solely one of these, can be related to our observations. It is worth highlighting, in the case caused by ischemia-reperfusion, that there is evidence in the literature on the protective effects that this therapy provides in ischemia-reperfusion on small intestine in murine models this through the confirmation of molecular and histological test [38]. Although we present only four cases of fulminant hepatitis, the results are promising and respond to the abundant evidence found in the current literature concerning the potential benefits of a targeted pharmacological strategy with PTX in this specific pathology, because these patients survived the event. It is noteworthy that, during the management of the patients, there were no severe adverse effects to the PTX, which occur only in 3% of patients according to that reported in the literature. Therefore, no patient abandoned treatment, this being an important factor to consider when handling this type of critical patients, in addition, and mainly due to that these were pediatric patients for whom we must increase safety measures, these data are in agreement with our own observations on children with leukemia. Another important characteristic of PTX is that is accessible and easy to use, and it is not expensive.

Finally, it is important to consider that the incidence of fulminant hepatitis, fortunately, is very low, and the ideal treatment of hepatic transplant is not possible in the majority of cases. Due to that and, based also on the low toxicity of the treatment, it results as convenient, considering that, in the worst case, even if the usefulness of PTX is not confirmed, it is, nonetheless, not toxic.

CONCLUSION

In conclusion, it is suggested that this novel alternative is encouraging for this potentially fatal entity where other effective and accessible alternatives are not available, which is why multicenter and randomized studies are suggested to assess its real efficacy.

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