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The Effect of Single Adminstration of Hydrocortisone in the Treatment of Severe Hyperbilirubinemia in Viral Hepatitis A: A Retrospective Study

Alena Koscalova[1,2]*, Peter Sabaka[1]*, Maria Sarvasova[1], Sena Stary[1], Matej Bendzala[1], Katarina Holeckova[1,2], Ioana Mozos[3,4], Robert Prosecky[5], Peter Kruzliak[6], Igor Stankovic[1]

[1]Department of Infectology and Geographical Medicine, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia.

[2]Faculty of Medicine, Slovak Medical University in Bratislava, Bratislava, Slovakia.

[3]Department of Functional Sciences, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania.

[4]Center for Translational Research and Systems Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania.

[5]2nd Department of Internal Medicine, Faculty of Medicine, Masaryk University and St. Anne´s University Hospital, Brno, Czech Republic.

[6]2nd Department of Surgery, Faculty of Medicine, Masaryk University and St. Anne´s University Hospital, Brno, Czech Republic.

*Co-first / Co-equal authorship

***Corresponding Authors:** Dr. Peter Kruzliak, Department of Internal Medicine, Brothers of Mercy Hospital, Polni 3, 63900 Brno, Czech Republic.*

Dr. Peter Sabaka, Department of Infectology and Geographical Medicine, Faculty of Medicine, Comenius University and University Hospital, Limbová 2645/5, 833 05 Bratislava, Slovakia.

Abstract

***Background:** Short courses of oral corticosteroids are effective in treating severe hyperbilirubinemia in patients with cholestatic course of viral hepatitis A (VHA). The effect of a single dose of parenteral hydrocortisone has not been described yet.*

***Methods:** We conducted a retrospective study of patients with VHA and severe hyperbilirubinemia (total bilirubin ≥ 200 µmol/l) lasting more than 7 days who received 100 mg of hydrocortisone comparing them to cohort of patient treated by standard symptomatic treatment.*

***Results:** Analysis included data from 46 patients with VHA, 9 of them (19.6%) received a single dose of hydrocortisone (SDH). Times to 25% and 50% decrease of total bilirubin was 4 days (3-5) and 5 days (3-8) in patients that received SDH and 7 days (4-9) and 7 days (9-13) in patients that only received symptomatic treatment. The time difference between both groups was significant for both 25% and 50% decrease of the total bilirubin ($p > 0.05$). In multivariate regression, SDH administration was negatively associated with time to 25% decrease of total bilirubin ($\eta p^2 = 0.222$, 95% CI: -15.687 - -2.944, $p > 0.05$) and time to 50% decrease of total bilirubin ($\eta p^2 = 0.171$, 95% CI: -14.181 - -0.228, $p > 0.05$) but was not associated with bilirubin concentration at the time of discharge from hospital.*

No side effects or complications of hydrocortisone administration were documented.

***Conclusions:** Administration of SDH was associated with more rapid decrease of plasmatic total bilirubin concentration in patients of VHA with severe hyperbilirubinemia.*

Keywords: *Viral hepatits A; corticosteroids; hyperbilirubinemia; hydrocortisone*

List of Abrevations

ALT: alanine aminotransferase

CI: confidence interval

cMOAT: canalicular multispecific organic anion transporter

CS: corticosteroids

Mrp2: multidrug resistance-associated protein 2

SDH: single dose hydrocortison

SHB: severe hyperbilirubinemia

VHA: viral hepatits A

Introduction

In European high-income countries, incidence of acute viral hepatitis A (VHA) is regarded to be low [1, 2]. However, in the past decade, several community-wide outbreaks have been documented. They originated from high risk groups (homeless, illicit drug abusers, very low-income earners) with secondary spreading to the general population by person to person transmission [3]. In low endemicity countries, the average age of cases is usually considerably higher than in high endemicity countries [1-3]. VHA is typically a benign and self-limiting disease, manageable by symptomatic therapy. However, the clinical course and prognosis differ significantly among different age groups [4]. Especially in older adults, severe hyperbilirubinemia (SHB) is relatively frequent. In SHB, bilirubin increases to very high levels at the time when transaminases are already decreasing. This increase usually does not correspond to the level of hepatocellular injury and has a significant cholestatic component [4, 5]. In about 1 to 10% of all VHA cases, hyperbilirubinemia and icterus lasts more than 3 months which is called severe prolonged cholestasis. Because of the higher age of VHA cases in developed countries, the occurrence of SHB is significantly higher [4-8]. The occurrence of SHB increases cost and duration of treatment thereby significantly burdening medical facilities during outbreaks. In general, corticosteroids (CS) are not recommended in the treatment of VHA, because its administration in an unselected population was not associated with better outcome [9-11]. On the other hand, several case reports [12-14] and one small clinical trial [15] documented the effect of oral CS therapy on faster resolution of jaundice and pruritus in patients with SHB. However, the use of CS is associated with the risk of various side effects which have been also documented in patient with VHA [15]. Therefore a prolonged use of steroids in VHA remains controversial and has to be limited to cases with severe prolonged cholestasis. The authors argue that the administration of a single dose of CS is associated only with few side effects and complications [16, 17] and might therefore be an alternative for patients with high and prolonged hyperbilirubinemia during the VHA course. However, to the authors' knowledge, the effect of SDH on bilirubin decrease during the VHA course has not been studied yet. We conducted retrospective study using data from patients hospitalised with VHA and SHB, comparing the rate of decrease of total bilirubin in patients receiving SDH to those that only received symptomatic treatment.

Methods

Patients

We conducted a retrospective cohort study of patients with VHA hospitalized at the Department of Infectology and Geographical medicine, University Hospital in Bratislava during the outbreak of Hepatitis A in Bratislava in 2017 and the first quarter of 2018. The data was obtained retrospectively from the files of patients and laboratory records. An Excel database has been developed to support the collection of the selected data.

VHA was diagnosed on the basis of positive class IgM antibodies against hepatitis A virus (HAV) and clinical presentations of acute hepatitis. For the purpose of this study, SHB was defined as level of the total bilirubin ≥ 200 µmol (11,70 mg/dl) at the time when ALT was bellow 8,5 µkat (500 IU/ml). Patients having history of liver cirrhosis, oncologic disease (except long term remission ≥ 5 years without clinical relapse), HIV infection, cholangitis, cholecystitis and hemolytic anemia and those chronically treated with corticosteroids were excluded. All patients were treated by a standard symptomatic treatment (low fat diet, bisulepine to reduce pruritus and lactulosis as a prevention of encephalopathy). Beside the standard symptomatic treatment, some patients with VHA and SHB received one dose of corticosteroids (100 mg of

hydrocortisone intravenously). SDH administration was based on the medical consensus of the senior clinicians. The objective of the treatment was mainly to shorten the duration of severe hyperbilirubinemia which was usually associated with severe pruritus. SDH was administered in patients in which bilirubin continued to rise for longer than 7 days despite marked decrease of transaminases.

Blood Sampling, Processing and Analytic Methods

To assess plasmatic concentration of total bilirubin, blood specimen was drawn after an overnight fast (at least 12 h) by venipuncture from cubital vein using the Vacutainer closed system with serum clot activator. After drawing blood, the blood specimens were left at room temperature for 30 min and subsequently a supernatant separated by centrifugation for 10 min at 3,000 rpm was analyzed. Total bilirubin concentration was determined by an enzymatic colorimetric method (Cobas Integra Bilirubin total gen.3, Roche Diagnostics GmbH, Montclair, NJ, USA).

Analysis of Effects of Hydrocortisone Administration

To evaluate the effects of SDH on the plasmatic level of the total bilirubin we compared time to 25% and 50% decrease of the total bilirubin in patients that received SDH to those that only received symptomatic treatment. Time to 25% and 50% bilirubin decrease were defined as number of days till the bilirubin concentration reached the levels less than 75% and 50% of the peak value.

Statistical Analysis

The quantitative variables between cohorts were compared using Mann-Whitney test because of the lack of normal distribution. Normal distribution was assessed using Shapiro-Wilk test. The effect of hydrocortisone administration on time to 25% and 50% decrease of the bilirubin was assessed using multivariate general linear model. Age, gender, peak bilirubin concentration, mean time between bilirubin mesurements, peak ALT concentration and length of hospitalization were included in the model as possible confounders. Statistical analysis was performed using SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.

Ethics

This study was carried out in concordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by local ethical committee. The investigators preserved full anonymity of all participants.

Results

Between January 2017 and March 2017, 207 patients with VHA were hospitalized at the Department of Infectology and Geographical medicine, University Hospital, Bratislava. 59 patients (28.5%) had a total plasmatic bilirubin over 200 μmol/l during the course of hospitalization. 13 patients (22%) with at least one exclusion criteria have been excluded from further analysis. 46 patients (36 men and 10 women) with severe cholestatic course of VHA were included in the analysis. 9 patients (5 men and 4 women) 19.6% received SDH. Table 1 summarize main characteristics of the patients included in the analysis.

The median time between admission to hospital and SDH administration was 9 days, same as the time to peak bilirubin in SDH cohort. In the group of patients receiving SDH, times to 25 % and 50% decrease of the peak bilirubin concentration were significantly lower (tab. 1). SDH group and the control group did not differ significantly in any other variables (tab. 1). In multivariate regression, SDH administration was negatively associated with both times to 25% and 50% decrease of the peak bilirubin. There was no significant difference between both groups in the total bilirubin concentration at the time of discharge (tab. 2). Time to 25% decrease of peak bilirubin was also negatively associated with male gender and time to 50% decrease was positively associated with age and peak ALT (tab. 2). In all patients in SDH cohort, total bilirubin concentration was continuously increasing until the hydrocortisone has been administered. After single dose hydrocortisone administration, total bilirubin concentration started decreasing steadily. No side effect or complication of SDH administration was documented during hospitalization. No patient from SDH or control cohort suffered relapse during follow up and none had liver failure.

Table1. *Basic characteristics of cohorts*

	SDH, n = 8	Control, n = 38	p	95% CI
Age (years)	48 (41-59)	49 (38-59)	0.977	-8.069 – 7.847
Days to peak bilirubin (days)	9 (5-12)	6 (2-8)	0.309	-2.301 – 7.189
Days to 25% decrease (days)	4 (3-5)	7 (4-9)	< 0.05	0.80 - 5.459
Days to 50% decrease (days)	5 (3-8)	7 (9-13)	< 0.05	1.986- 9.064
Peak total bilirubin (μmol)	270 (212-426)	269 (235-423)	0.718	-74.005 – 103.589
Peak ALT (μkat)	56 (35-116)	45 (29-81)	0.277	-18.950 – 59.055
Hospitalization duration (days)	14 (12-21)	13 (10-16)	0.600	-3.309 – 5.531
Total bilirubin at the time of discharge from hospital (μmol)	111 (75-186)	147 (77-216)	0.881	-88.468 – 67.328
Mean time between bilirubin mesurements (days)	4 (2-6)	4 (2-5)	0.961	-0.653 – 1.367

Variables provided as median (25^{th} -75^{th} percentile), ALT- alanine aminotransferase, CI – confidence interval, n - number, p – probability (Mann-Whitney), SDH - single dose hydrocortisone cohort

Table 2: Association of time from peak total bilirubin to its 25% and 50% decrease and with total bilirubin at demission with other variables in multivariate analysis.: The effect of hydrocortisone administration on time to 25% and 50% decrease of the total bilirubin concentration and bilirubin concentration at the time of discharge was assessed using multivariate general linear model. Age, gender, peak bilirubin concentration, peak ALT concentration, mean time between bilirubin mesurements and length of hospitalization were included in the model as possible confounders.

Table2. *Association of time from peak total bilirubin to its 25% and 50% decrease and with total bilirubin at demission with other variables in multivariate analysis.*

	time to 25% decrease of total bilirubin after peak		time to 50% decrease of total bilirubin after peak		Total bilirubin at discharge from hospital	
	η_p^2	95% CI	η_p^2	95% CI	η_p^2	95% CI
SDH	0.222*	-15.687 - -2.944	0.171*	-14.181 - -0.228	0.064	-196.555 – 20.718
Age	0.051	-0.0.39 – 0.208	0.226*	0.056 – 0.398	0.147*	0.563 – 4.539
Gender (male)	0.223*	-11.273 - -2.695	0.002	-6.530 – 5.265	0.013	-97.438 – 45.819
Peak bilirubin	0.006	-0.16 - 0.025	0.024	-0.016 – 0.034	0.152*	0.105 – 792
Peak ALT	0.002	-0.33 – 0.043	0.206*	0.007 – 0.115	0.030	-0.290 – 0.969

ALT- alanine aminotransferase, CI - confidence interval, SDH – single dose parenteral hydrocortisone administration, η_p^2 – partial eta squared (measure of effect size), * $p < 0.05$

Discussion

This retrospective study demonstrated that administration of SDH in cases of VHA and severe hyperbilirubinemia is associated with more rapid decrease of plasmatic bilirubin as compared to patients receiving only symptomatic treatment.

Corticosteroids are not routinely recommended in treatment of VHA because of the lack of evidence about their effectiveness and concerns of side effects [9, 10]. Increase risk of relapses in patients receiving CS has also been documented [11]. On the other hand, beneficial effects of short courses of corticosteroids in severe cholestatic VHA patients have been documented in several case reports. Authors of these case reports described quick resolution of cholestatic jaundice after short course of oral CS. They concluded that CS therapy might be effective in alleviation of symptoms

in thoroughly selected patients with VHA and severe prolonged cholestasis [12-14]. Median times from administration of SDH to 25% and to 50% decrease of total bilirubin in our study approximately correspond with cases of VHA with severe prolonged cholestasis treated by prednisolone described in literature.

Jeffey at al. conducted small prospective randomized controlled trial comparing effects of oral prednisolone to ursodeoxycholic acid in patients with VHA and serum bilirubin of more than 10mg/dl. CS course consisted of 0.75 mg/kg/day of prednisolone for 4 weeks. The primary endpoint was the decrease of bilirubin concentration to 3 mg/dl. They observed faster decrease of bilirubin to target level in prednisolone arm [15]. The retrospective aspect of our study prevented the evaluation of the time taken for bilirubin to decrease to 3 mg/dl due to a significant number of patients being followed-up outside our facility after discharge. The exact time of reaching this threshold was therefore not obtained. Thus, our endpoints were chosen to be the decrease of bilirubin concentration by 25 % and 50% of the peak value. Therefore, our results are not fully comparable. However, as Jaffey at al. we observed that corticoid therapy is associated with a steeper decline of total bilirubin.

Another interesting observation obtained, was that the course of a bilirubin concentration curve shifted from constant increase to decrease after SDH administration in all of the patients. This is a noteworthy finding on its own.

Because of the short duration of follow up, we were unable to assess the effects of SDH on time to needed to reach normal bilirubin levels and thus we are unable to say if just single dose of hydrocortisone is enough to induce quicker normalization of total bilirubin concentration. It is possible, that more than one hydrocortisone administration would be needed to reach this goal. However, we can conclude that SDH is efficient in stimulating reduction of bilirubin by 50% and thus might be beneficial in patients with VHA and severe bilirubinemia. The faster decrease of bilirubin might significantly ease most of the troublesome symptoms associated with severe hyperbilirubinemia.

Safety of Corticosteroids in VHA

Another issue that must be taken into consideration is the risk of possible side effects and relapse of VHA associated with CS therapy. In the trial by Jeffey at al. prednisolone therapy was associated with several side effects like pedal edemas, acne vulgaris, facial puffiness and even more serious complications like steroid-induced acute pancreatitis [15]. According to large population based cross-sectional study, even a short course of corticosteroids is associated with significant risk of serious complications like venous thromboembolism, sepsis or major fractures [18]. Use of CS in VHA might be associated with higher risk of relapsing course of VHA [11]. Other prospective studies however did not confirm the increased risk of relapsing VHA associated with CS therapy [9, 10]. Concerns about possible side effects and relapses however lead to serious doubts, if benefits of short course of oral CS outweigh the risks if used in patients other than those with most severe cholestasis. On the other hand, single administration of moderate dose of corticosteroid is relatively safe compared to short courses of oral corticosteroids [16]. This favours the use of SDH in patients with severe hyperbilirubinemia, especially those, who do not yet fulfil the criteria for severe prolonged cholestasis, but suffer from prolonged hyperbilirubinemia not responding to symptomatic therapy.

Clinical Significance

The clinical course of VHA is usually benign and manageable by symptomatic therapy, especially in young patients with VHA. In older patients, there is common occurrence of cholestatic course of VHA complicated by severe pruritus, fatigue and anorexia. Also, in patients who don't meet the criteria for severe prolonged cholestasis but have prolonged high bilirubin levels, the clinical course is unpleasant and exhausting [4-6]. In developed countries, the incidence of VHA is low, but the patients with VHA are usually much older than in countries with high endemicity [2, 3]. Because of the higher age, the relative occurrence of VHA with prolonged severe hyperbilirubinemia is high [6]. Cases with VHA and severe hyperbilirubinemia usually requires longer hospitalization [3, 7] and during outbreaks might create significant burdens on already stretched medical facilities. Severe hyperbilirubinemia causes pruritus refractory to symptomatic therapy. If some of the CS regimes proves to be safe and effective in

reducing the duration of severe hyperbilirubinemia and thus the duration of hospitalisation it might also be helpful to provide some relieve from pruritus.

Pathophysiology of Cholestasis in VHA and Possible Effects of Corticosteroids

Cholestasis in viral hepatitis is believed to be induced by inflammation and proinflamatory cytokines [19-21]. CS therapy inhibits synthesis of proinflamatory cytokines by inhibition of NF-kappa B, which plays central role in expression of proteins associated with inflammation. It is believed that effects of liver inflammation on bilirubin excretion are mediated through canalicular multispecific organic anion transporter (cMOAT) or better known as multidrug resistance-associated protein 2 (MRP2). This transporter protein is necessary in the process of conjugated bilirubin transfer through hepatocyte membrane to the biliary space. It is well known that proinflamatory cytokines like TNF-α and IL-1 inhibits expression of Mrp2 gene [22, 23]. In a rat model of sepsis, administration of dexamethasone neutralise the effects of endotoxine on Mrp2 in liver. Another proposed pathway of CS mechanism of action might be independent of proinflamatory cytokines and inflammation activity. Dexamethasone enhances the expression of Mrp2 in rats [24]. This effect is apparently mediated directly since various corticoid responsive elements have been identified in promoter region of Mrp2 gene [25]. Interesting observation is that stimulation with single dose dexamethasone results in 4.5-fold increase in expression of Mrp2, which returns to prestimulation values in more than 6 days [26].

Study Limitations

The limitations of our study mostly originate from its retrospective design. Patients were not randomized, hydrocortisone administration has not been placebo controlled and no exact rules for SDH indication have been determined. SDH administration was based on the consensus of judgements of senior consultants to alleviate pruritus in cases of prolonged severe hyperbilirubinemia. Thus, hydrocortisone was administered to the most severe cases of VHA. Considering these limitations, selection bias cannot be ruled out completely. To minimize effects of possible confounders, we performed multivariate analysis including variables associated with VHA severity. In more severe cases, we can hardly expect quicker decline of bilirubinemia, so we are confident in the conclusion that this factor is not responsible for the result we obtained. Because of the lack of randomization and the different composition of cohorts, we are unable to fully compare our results with the result of prospective study by Jeffey et al. The study design did not allow us to evaluate the time to decrease of bilirubin to 3 mg/dl because after demission, a significant number of patients was followed up outside our facility and the exact time of reaching this threshold was not obtainable. Because of the same reason, we were unable to determine how many of our patients met the criteria for severe prolonged cholestasis (hyperbilirubinemia lasting more than 3 months). However, Jaffey at al. were facing similar problems. The mean duration of hyperbilirubinemia in their cohorts was far less than 3 months [15]. Because our study population lacks the cohort of patients treated by short course of oral corticosteroids, we are unable to compare its effectiveness and safety to SDH. Nevertheless, despite the limitations of our study, according to our results, we can conclude that SDH administration is associated with more rapid decrease of plasmatic bilirubin concentration by one half of its peak concentration.

Conclusions

One single parenteral dose of 100 mg of hydrocortisone is associated with more rapid decrease of plasmatic total bilirubin concentration by 25 and 50% and sharper decline after reaching peak value in cases of VHA with peak plasmatic bilirubin concentration ≥ 200 μmol. However, because of the limitations originating from retrospective design, prospective randomized trials will be necessary to assess effectiveness and safety of single dose hydrocortisone administration in the management of severe hyperbilirubinemia in VHA.

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