

Effect of Amlodipine on Hepatitis C Virus Induced Portal Hypertension in Children with Acute Leukemia

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ABSTRACT

Background: Children with acute leukemia are at high risk of hepatitis C infection, either by immunosuppression secondary to chemotherapy or by multiple transfusions of blood products during the course of the disease. Hepatitis C constitute a major problem during management of acute leukemias due to resultant Portal hypertension, or bleeding esophageal varices. Chronic HCV infection is a major cause of liver cirrhosis and hepatocellular carcinoma in leukemic survivors.

Aim: In the present study we tested the effect of Amlodipine on children of acute lymphoblastic leukemia having portal hypertension secondary to hepatitis c infection during maintenance chemotherapy

Results: From this study, we found that Amlodipine was effective in reducing the elevated portal blood pressure to normal level in doses which doesnot interfere with mechanism of action of chemotherapy

Conclusion: Treatment with Amlodipine can be used to control portal hypertension in leukemic children having hepatitis c virus induced portal hypertension.

INTRODUCTION

Children with leukemia are at high risk of HCV infection due to the large transfusional support they often needed and to the immunodeficiency status caused by either the underlying disease or by chemotherapy¹.

Before the discovery of the hepatitis C virus (HCV) and the implementation of anti-HCV tests for the screening of blood donors, at that time, about 70% of children with acute leukemia were found to have a persistent elevation of transaminase levels with liver histologic lesions suggestive of chronic viral hepatitis that, could be related to hepatitis B virus infection in about half of the children, the remaining being cases of non-A, non-B hepatitis².

More recently, several studies based on the detection of HCV markers in serum, mainly anti-HCV by enzyme-linked im-

munosorbent assay (ELISA), have reported variable prevalences of positive HCV serology in this clinical setting, in association with a wide spectrum of liver involvement, ranging from minimal enzyme elevation to severe, life-threatening hepatic failure³. Most patients, however, were found to have a persistent elevation of transaminase levels with no significant impairment of liver functions.

The high rate of chronic hepatitis in this clinical setting has become a major concern for the long-term outcome of the patients, as the prognosis of childhood leukemia has dramatically improved over the last 20 years, while chronic HCV infection has been recognized as a major cause of liver cirrhosis and hepatocellular carcinoma⁴. Data are limited regarding the effects of immunosuppression on viral load and severity of liver disease in long-term anti-HCV positive leukemia survivors. However, others, have shown that HCV RNA levels increase as the immune deficiency progresses. Coinfection with other viruses such as CMV, EBV have also been shown to be associated with an increased risk of cirrhosis and liver failure. Conversely, long-term follow-up of immunocompetent individuals has shown only a small increase in deaths related to liver disease⁵.

On the other hand, many medications have been evaluated and used in treatment of hepatitis c induced complications, all were focusing on reducing resultant portal hypertension as propranolol and/or isosorbide mononitrate^{6,7}. The use of calcium channel blockers in treatment of portal hypertension was examined. Four calcium channel blockers were tried: nifedipine, verapamil, cinnarizine and tetrandine. They found to significantly reduce the esophageal variceal pressure, portal venous pressure and portal blood flow in cirrhotic patients with portal hypertension. There is few literatures about the use of amlodipine in treatment of portal hypertension. Amlodipine is a long acting calcium channel blocker of the dihydropyridine group which has

no hepatotoxic effect. The drug is favourably used in treating cardiovascular diseases^{8,9}.

SUBJECTS AND METHODS

Thirty male children with acute lymphoblastic leukemia in remission were included in this study. All of them have hepatitis c infection confirmed with real time PCR but not invasive liver biopsy, but none of them exhibit any signs of liver decompensation, or bleeding oesophageal varices.

We had chosen male (♂) children and not female (♀) children to avoid the effect of female sex hormones on the smooth muscles of blood vessels. All patients were selected from outpatient clinic of pediatrics in Mansoura University oncology centre according to:

Inclusion criteria:-

- ages >10 years old (mean age was between 10.83±1.1 and 11.8±1.0 years), weight between 25-30 kg
- The bone marrow in complete remission (blast cells ≤ 5)
- remission under maintenance chemotherapy of leukemia was ≥ 1 year
- No signs of liver decompensation

Written consent was obtained from parents of children prior to take amlodipine

Patients were given amlodipine for 6 months during the maintenance chemotherapy but not on the same day to avoid vomiting, maintenance chemotherapy consisted of oral 6 mercaptopurine, oral methotrexate, intravenous vincristine

Patients were divided into 3 groups:

Figure 1: Systemic blood pressure, heart rate, portal blood pressure and liver & spleen span in normal and treated children. (group 1 and 3)

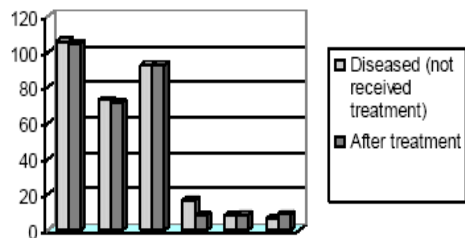
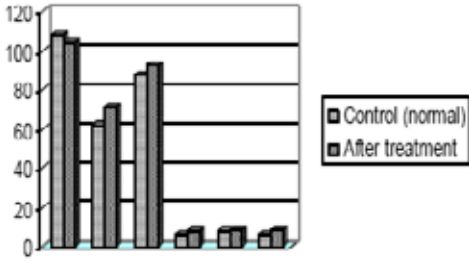


Figure 2: Systemic blood pressure, heart rate, portal blood pressure and liver & spleen span in diseased (not received treatment (group2) and treated children(group3).



i) Group 1: consisted of 15 children considered as normal control group and they did not received any therapy. They were exposed to estimation of systemic blood pressure and heart rate clinically while portal blood pressure and liver & spleen span were estimated by ultrasonography. Doppler Flow Study was done to measure the flow of blood through a blood vessel.

ii) Group 2: consisted of 15 children with acute leukemia in remission suffering from portal hypertension secondary to infection by hepatitis C and they had positive serology of hepatitis C antibodies, all were confirmed with real time PCR but not liver biopsy. Placebo therapy was given to this group.

iii) Group 3: consisted of 15 children with acute leukemia in remission suffering from portal hypertension secondary to infection by hepatitis C and they had positive serology of hepatitis C antibodies all were confirmed with real time PCR but not liver biopsy and treatment was given to this group in the form of Amlodipine (Norvasc) orally once/day for four weeks. It was provided in the form of tablet (5 mg).

The dose of Amlodipine was equivalent to that used in adult according to equation¹⁰.

$$\text{Approximate dose in children} = \frac{\text{Surface area of child (m}^2\text{)}}{1.8 \times \text{adult dose (1.7 mg)}}$$

The second and third groups were exposed

to the same investigations as the control group before and after taking Amlodipine therapy. All three groups were maintained on their usual dietary habits and their usual daily activities, and they were instructed not to stop chemotherapy.

Hepatitis C Virus (HCV) antibody detection: Anti HCV was detected using HCV 3rd generation EIa Kit from Abbott (Wiesbaden, delRnheim, Germany) following the manufacture’s instructions.

HCV RNA detection: HCV RNA was detected by RT-PCR using Biosewoom HCV PCR kit (from Biosewoom Inc. Seoul Kotea). Total RNA was prepared from serum samples according to the manufacture’s instructions.

Statistical analysis:

Statistical analysis was performed using unpaired and paired test by SPSS program (Statistical package for social science) version 10 (1999).

RESULTS

A significant increase was found blood pressure ($p < 0.05$) in the diseased group 2 compared to control normal group 1. On the other hand, non significant change was detected in systemic blood pressure, heart rate, liver, and spleen span in the diseased group2 compared to the normal group ($p > 0.05$). Table (1)

Group 3 showed significant decrease in portal blood pressure levels ($p < 0.05$) after treatment with amlodipine compared to portal blood pressure levels before treatment. On the other hand, non significant change was evident in systemic blood pressure, heart rate, liver, and spleen span ($p > 0.05$) after treatment with amlodipine compared to their values before treatment. Table (2)

Portal blood pressure levels in group 3 children treated with amlodipine were significantly higher from the levels in the control normal group 1. Moreover, an insignificant difference in systemic blood pressure, heart rate, liver, and spleen span was observed between normal and treated children ($p > 0.05$). Table (3)

Table 1: Comparison of systemic blood pressure, heart rate, portal blood pressure, liver, and spleen span in between group I, and group II (not receiving any therapy).

Parameter	Group I (control) n=15	Group II n=15	p value
Systolic B.P (mmHg) Mean ± SD	108.08 ± 7.51	106.07 ± 10.40	>0.05
Diastolic B.P (mmHg) Mean ± SD	71.92 ± 6.00	72.86 ± 9.37	>0.05
Heart rate (beats/min) Mean ± SD	97.93 ± 5.03	92.86 ± 7.27 P>0.05	>0.05
Portal B.P (mmHg) Mean ± SD	6.12 ± 0.51	14.41 ± 1.10*	<0.05*
Liver span (cm) Mean ± SD	8.14 ± 0.80	7.93 ± 0.27	>0.05
spleen span (cm) Mean ± SD	6.36 ± 0.63	6.29 ± 0.62	>0.05

Table 2: Effect of Amlodipine on systemic blood pressure, heart rate, portal blood pressure, liver, and spleen span in group III children after III months of treatment.

Parameter	Group III before treatment (n=15)	Group III after treatment (n=15)	p value
Systolic B.P (mmHg) Mean ± SD	105 ± 10.11	104.64 ± 9.04	>0.05
Diastolic B.P (mmHg) Mean ± SD	70.71 ± 6.84	71.43 ± 7.09	>0.05
Heart rate (beats/min) Mean ± SD	93.93 ± 5.3	92.92 ± 5.87	>0.05
Portal B.P (mmHg) Mean ± SD	15.11 ± 1.50	8.08 ± 0.74*	>0.05*
Liver span (cm) Mean ± SD	8.17 ± 0.79	8.13 ± 0.22	>0.05
spleen span (cm) Mean ± SD	6.62 ± 0.16	8.57 ± 0.15	>0.05

Table 3: Comparison of systemic blood pressure, heart rate, portal blood pressure, liver, and spleen span between group I and group III after amlodipine treatment.

Parameter	Group I (n=15)	Group III after treatment (n=15)	p value
Systolic B.P (mmHg) Mean ± SD	108.08 ± 7.51	104.64 ± 9.04	>0.05
Diastolic B.P (mmHg) Mean ± SD	71.92 ± 6.00	71.43 ± 7.09	>0.05
Heart rate (beats/min) Mean ± SD	97.93 ± 5.03	92.92 ± 5.87	>0.05
Portal B.P (mmHg) Mean ± SD	6.12 ± 0.51	8.08 ± 0.74*	>0.05
Liver span (cm) Mean ± SD	8.14 ± 0.80	8.13 ± 0.22	>0.05
spleen span (cm) Mean ± SD	6.36 ± 0.63	8.57 ± 0.15	>0.05

Table 4: Comparison of systemic blood pressure, heart rate, portal blood pressure, liver, and spleen span between group II and group III after amlodipine treatment.

Parameter	Group 2 (n=15)	Group 3 after treatment (n=15)	p value
Systolic B.P (mmHg) Mean ± SD	106.07 ± 10.40	104.64 ± 9.04	>0.05(0.8)
Diastolic B.P (mmHg) Mean ± SD	72.86 ± 9.37	71.43 ± 7.09	>0.05(0.8)
Heart rate (beats/min) Mean ± SD	92.86 ± 7.27	92.92 ± 5.87	>0.05(0.9)
Portal B.P (mmHg) Mean ± SD	14.41 ± 1.10	8.08 ± 0.74*	<0.05*(0.0003)
Liver span (cm) Mean ± SD	7.93 ± 0.27	8.13 ± 0.22	>0.05(0.3)
spleen span (cm) Mean ± SD	6.29 ± 0.62	8.57 ± 0.15	>0.05(0.3)

Portal blood pressure levels in group 3 children after treatment with amlodipine recorded significantly lower levels than that of untreated children in group 2 ($p < 0.05$). In addition, a non significant difference in systemic blood pressure, heart rate, liver, and spleen span was found in untreated children of group 2 compared to treated children of group 3 ($p > 0.05$). Table (4) and figure (2)

DISCUSSION

Data are limited regarding the effects of immunosuppression on viral load and severity of liver disease in long-term anti-HCV positive leukemia survivors. However, numerous investigators have reported that anti-HCV positive individuals during follow up little develop symptoms of liver cell failure or decompensated liver disease, instead they developed chronic hepatitis which hinder the process of continuous administration of chemotherapy. Portal hypertension may be developed as a side effects of drugs regimen used as maintenance therapy of leukemia itself, as Broxson et al,¹¹ stated that portal hypertension develops in children with lymphoblastic leukemia treated with 6- thioguanine during maintenance therapy. Owing to the results in Broxon study, portal hypertension recorded was of the moderate degree with no evidence of splenomegaly or hepatic cirrhosis. Many drugs have been used to lower the elevated portal blood pressure as

beta blockers (propranolol) and nitroglycerine. In the present study we tested the effect of a long acting calcium channel blocker (Amlodipine) on pediatric portal hypertension induced by hepatitis c virus infection as the usage of Interferon during chemotherapy is warranted.¹²

Amlodipine is a calcium channel blocker of the dihydropyridine group which has no hepatotoxic effect^{9,13-14}. The results of this study were promising. we found that Amlodipine produced a significant drop in pediatric portal hypertension at doses which did not produce any effect on the systemic blood pressure or the heart rate. Previous study done by Li, 1991¹⁴ (demonstrated that nifedipine, verapamil and cinnarazine could significantly reduce the esophageal variceal pressure, portal venous pressure and portal blood flow in cirrhotic patients with portal hypertension.

Furthermore, he found that neither heart rate nor blood pressure showed any significant change in spite of pressure reduction. Suga et al.,¹⁵ demonstrated that nifidipine and verapamil reduced the KcL – and nor-epinephrine induced contraction of the portal vein to a greater extent than they relaxed those of mesenteric artery and they recommended the use of calcium channel blockers in treatment of portal hypertension. Dine et al.,¹⁶ mentioned that verapamil appears to

have splanchnic, portal, splenic, portocolateral and probably intrahepatic venodilator effects in patients with advanced posthepatic liver cirrhosis. Moreover, verapamil caused an increase in the liver blood flow¹⁷ while diltiazem reduced portal pressure in patients with non cirrhotic portal fibrosis^{17,18}.

On the other hand, Bruges and Moisey⁸ found that although Amlodipine appears to bind to additional calcium channel recognition sites blocked by diltiazem and verapamil, it does not significantly depress heart rate and does not produce significant negative inotropic effects or electrophysiologic disturbance

Amlodipine does not significantly affect sinus node function, cardiac conduction, or have negative inotropic effects at clinical doses. The gradual pharmacological effect of amlodipine does not produce tachycardia caused by other peripheral vasodilators. Serum calcium levels are unaffected by Amlodipine.

The reduction in portal pressure observed in the study could be explained by the relaxant effect of Amlodipine on vascular smooth muscle due to blockade of the voltage dependent calcium channel of the L-type^{13,14}. Amlodipine selectively inhibits the transmembrane influx of calcium ions into the vascular smooth muscle. A decrease in intracellular calcium inhibits the contractility of the smooth muscle cells. This results in the dilation of blood vessel with a greater pharmacological effect on the vascular smooth muscle than the cardiac muscle resulting in a reduction in the peripheral vascular resistance and the blood pressure^{13,14}.

This study suggests that Amlodipine treatment is well tolerated in children with portal hypertension and provides sustained blood pressure control. Further studies are necessary to determine if the calcium channel blocker treatment can have any effect on growth and development of children having portal hypertension, or any effect on leukemic process and remission state.

CONCLUSION

Treatment with Amlodipine can be used in controlling portal hypertention in patients having hepatitis c virus induced portal hypertention together with the treatment of leukemia.

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