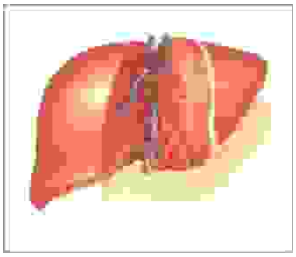
ORIGINAL PROF-759

ROLE OF AMANTADINE IN TREATMENT OF CHRONIC HEPATITIS C



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SUMMARY... drkamin2002@yahoo.com **Background:** Interferon afla (IFN-alfa) is the only effective treatment for patients with Chronic hepatitis C. Forty percent of patients have an initial response to therapy. But most subsequently relapse. Amantadine, an antiviral agent, in addition ability, of preferably concentrating in liver , has shown a role in reducing hepatic inflammation and suppressing viral replication . The aim of this study was to assess the efficacy and safety Of amantadine for treatment of chronic infection with hepatitis C virus (HCV). **Design:** Prospective study. **Period:** From January 2002 to Dec 2003, **Setting:** Allied Hospital, Faisalabad. **Methods:** Fifty patients either naive or interferon resistant, with age range of 18-65 years. were enrolled and treated with amantadine 100mg orally twice daily for six month. Control groups included the same cohort followed of therapy for 12-18 month or during therapy with interferon .All patients were assessed for safety. Tolerance and efficacy at the end of every month during treatment was completed. Patients were followed up for an additional six month to assess durability of response. The primary end - point were loss of detectable HCV-RNA six month after cessation of therapy. **Findings:** Out of 50 patients treated for six months with amantadine compared to intervals without therapy or to interferon therapy,17 (34%) had normal serum alanive aminotransferase (ALT)values and had cleared HCV RNA in serum by the end of treatment . The sustained virological response was found in 11patients with an undetectable serum HCV RNA level six month after therapy Baseline low serum HCV RNA levels were associated with higher rates of Response . During the therapeutic trial, amantadine caused no potential treatment limiting side effects but had a good safety profile. **Interpretation:** Therapy with amantadine results in biochemical as well as virological response both in the naive and interferon resistant cases of chronic hepatitis C.

INTRODUCTION

The hepatitis C virus (HCV) first described in 1989. Was responsible for most cases of post - transfusion associated hepatitis or non -A non-B hepatitis[1]. Seropositivity to hepatitis C occurs in approximately 0.4-2% of the U.S population and accounts for the overwhelming majority of cases of chronic hepatitis. Our understanding of the natural history of chronic hepatitis C disease, is evolving[2].

Hepatitis C infection is associated with the development of advanced liver disease and hepatocellular carcinoma and liver failure due to hepatitis C infection is the most common indication for liver transplantation in many centers[3].

Currently, the only approved treatment for chronic hepatitis C is interferon. Utilizing the standard therapy of 3 million units subcutaneously three times weekly, for six months, approximately 50% respond with normalization of alanine amino-transferase (ALT)[2]. Unfortunately ,half of those responding will relapse upon discontinuation of therapy[4].

Most who are retreated will again relapse after drug withdrawal. in patients who do not respond to the initial interferon therapy, dose escalation has been attempted with little success[5].

Higher dose regimens result in an increased incidence of side effects including flu like symptoms, depression, alopecia. And granulocytopenia. While longer duration of therapy with interferon is being advocated by some groups, complete response occurs in only one third of patients after 18 months of therapy[6].

The low response rate with interferon as well as the high occurrence of side effects has prompted investigators to search for other drugs that may be efficacious in the treatment of hepatitis C. Amantadine, a drug developed in the 1960s has diverse uses ranging from prevention of influenza a infection to the treatment of parkinson , s disease [7].

The antiviral mechanism of action is not thoroughly understood , however , amantadine has been shown to block events in late viral uncoating or early transcription[8]. While few studies have reported the tissue distribution of amantadine. The ability to achieve high liver concentraction along with its antiviral properties explain why amantadine may be effective in patients with hepatitis C infection . It has been tried with success in patients with hepatitis C who had previously not responded to treatment with interferon[9].

PURPOSE OF STUDY

To evaluate the efficacy and safety of amantadine as a mono-therapy both in the naive and interferon resistant cases of chronic hepatitis C.

MATERIAL AND METHODS

study design

An open labeled ,single arm, prospective study.

Study population

Fifty patients were selected on the basic of criteria mentioned below. The same cohort was studied as control for 12-18 month while on (interferon) therapy or taking us treatment.

INCLUSION CRITERIA

1. Patient of either sex with age range of 18-65 years.
2. Evidence of hepatitis C virus infection, as indicated by:
   a. Increased level of serum ALT on at least two of three occasions in the preceding 6 month.
   b. Detection of HCV-RNA by PCR.
   c. Serum positivity for anti-HCV antibody.
3. Evidence of chronic liver disease on ultrasonography.
4. All the cases either newly diagnosed or previously on interferon therapy who did not respond to treatment or experienced significant side effects, were included in the study log.

5. Histological diagnosis of chronic liver disease including early stages of cirrhosis(optional).

EXCLUSION CRITERIA

1. Evidence of decompensated liver disease:
   a. prothrombin time greater than 2 sec over control .
   b. Serum albumin less than 3.5gm/dl.
   c. History of hepatic encephalopathy, vericeal bleeding or ascites.
2. Other forms of chronic liver disease such as auto-immune hepatitis, hepatitis B, alcoholic liver disease, sclerosing cholangitis, biliary cirrhosis or drug related hepatotoxicity
3. Severe medical or surgical condition compromising the benefits of study.
4. Co-infection with HIV.
5. Concomitant HBV and HCV infection.
6. History of psychiatric illness.
7. History of pregnancy or lactation.

CONSENT

A written informed consent was obtained from every patient enrolled for study purpose.

TREATMENT PROTOCOL

Patient were treated with amantadine HCL 100mg orally twice daily for six months. No significant adverse event requiring reduction in dose or withdrawal of therapy was documented and the treatment was completed by all the patients.

ASSESSMENT AND MONITORING

Preliminary Assessment

All the patient selected for research protocol were assessed prior to start of therapy as follows:

1. A through physical examination.
2. Medical history.
3. Full blood count and chemistry including platelet count serum ALT asparate aminotransferase, alkaline phosphatase, total bilirubin, serum albumin, electrolytes, urea and creatinine.
4. Determination of HCV-RNA values in serum (qualitative and quantitative).
5. Detection of concurrent HIV and HBV infection.
6. Screening for pregnancy in case of woman of child bearing age.
7. Liver biopsy (optional).

On Study Evaluation and Follow-up

For analysis patient were divided into one of three groups based upon response in ALT and HCV-RNA values.

Responders. Normalization of ALT and loss of HCV-RNA.

Partial responders: more then 50%reduction in ALT & HCV–RNA compered to the pretreatment values. Although patients in this group showed virologic and biochemical response, but did not clear HCV-RNA completely, so they were considered treatment failures and included in the now -responder group.

Non-responders: Either no response or less than 50% reduction in ALT and HCV-RNA values compered to pretreatment levels

A physical examination, symptom analysis, and lab outlined earlier were performed monthly while on the drug, and six month after stropping therapy. PCR for HCV-RNA (qualitative and quantitative) was repeated at three months, at the end of therapy and six months after completion of therapy to assess to durability of response.

RESULTS

The present study was conducted in 50 patients during a period from January 2002 to Dec 2003, at Allied Hospital, Faisalabad. 41 out of 50 patients. (82%) were newly diagnosed and 9 patients (18%) were interferon resistant who had shown no response 2(14%) or left the treatment due to severe side effect of (interferon) therapy. The baseline characteristics of the patient are shown in table I. The age range was 24 to 61 years with major bulk of patient (74%) in the age group between 31 and 55 years. Amongst the study sample, 28 patients (56%) were males and 22

(44%) were females . The mode of acquisition of hepatitis C virus infection was blood transfusion in 34 patients (68%), parental drug use in 10 patients (20%) and sporadic or unknown in 6 patients(12%).

Most of the cases were from Faisalabad city (58%) while the other came from suburbs of Faisalabad , including 7 from Jhang, 5 from Toba Tek Singh, 4 from Gojra , 2 from Chiniot and one each from Kamalia, Samundari and Jaranwala

Symptoms on presentation were generally non-specific such and fatigue (28%), pain epigastrium (20%) dyspepsia (14%), flatulance (10%) and anxiety related symptoms (8%) . Six patient (12%) had no symptoms, while four of the interferon resistant cases (8%) had symptoms of anorexia and pain right hypochondrium.

The findings on preliminary examination were palmar erythema in 3 patients (6%), hepatomegaly in 14 patients (28%) and splenomegaly in 4 patients (8%). No patient with flapping tremor , deep jaundice or ascites was included in the study in accordance with exclusion criteria .

Pretreatment liver biopsy specimens were available from 32 patients sixteen patients refused to undergo biopsy, including the four with splenomegaly, and two had inadequate biopsy specimens. On histopathological examination, the disease activity was mild in 6 patients (knodell HAI:4-8),moderate in 21 patients (knodellHAI:9-12) and severe in 5 patients (knodell HAI:13-18). Fibrosis score was 1 in 22 patients and 11 in 10 patients .

VIROLOGICAL RESPONSE

Serum HCV-RNA levels became undetectable by the end of treatment of 17 of the 50 patients . HCV-RNA levels remained undetectable throughout the follow-up period (defined as a sustained virologic response) in 11 patients . Six patients again became reactive for HCV-RNA , one at the third month, two in the fourth month and three during fifth month after discontinuation of therapy.

Eighteen patients revealed a decrease in HCV-RNA levels but the values remained in the detectable range, they were labeled as partial responders (considered as non -responders) fifteen patients failed to respond to amantadine therapy and their HCV-RNA titre did not fall significantly.

BIOCHEMICAL RESPONSE

Serum ALT values were normal in 17 of the 50 patients by the end of treatment .Among the patients with such a response, the levels remained normal throughout follow -up in 13 patients and 4 patient showed a rise in concentration above the normal limits.

A fall in serum ALT values by more than 50% was observed in 18 patients but the levels remained abnormal (partial responders considered as non - responders) fifteen patients showed no response to therapy with persistently high serum alanine aminotransferase concentration .

CORRELATION OF BASELINE CHARACTERISTICS WITH RESPONSE

The pretreatment characteristics of patient according to response to amantadine are shown in table 2. The baseline HCV-RNA levels influenced the response to treatment with amantadine- responders had lower HCV-RNA levels compered to the non- responders. In contrast, the response was not influenced by the histologic findings at baseline, age , sex are the presumed source of infection.

OTHER LABORATORY FINDINGS

Response patterns of serum asparate aminotransferase were similar to those of serum alanine aminotransferase (data not shown). Hemoglobin concentration, white blood count, and platelets count remained stable throughout therapy and in follow -up. There was slight improvement in serum albumin concentration with treatment but the difference was not significant.

ADVERSE EVENTS

All the patient enrolled into the study were started on amantadine at a dose of 200mg daily in divided

doses. No serious side effect was observed during therapy which would need hospitalization or discontinuation of treatment. Some patient (16%) had minor neurological symptoms including insomnia , light headedness, difficulty in concentrating and headache. Other adverse effect like nausea, vomiting, dry mouth and urinary retention were not reported . Four patient complained of constipation which resolved with dietary fibre without any reduction in the dose of amantadine.

One patient developed chest pain while on therapy but his electrocardiogram (ECG) was normal and the pain settled with simple analgesics.

The pretreatment complaints of fatigue, anorexia and depression were improved and there was significant feeling of well- being during therapy compared to the period of no treatment.

Table-I. Baseline characteristics of the patients on enrollment

Age(years)	
-Mean	42.6
-Range	24-61
Male sex -no(%)	28(56)
Source of infection-no(%)	
-Blood transfusion	34(68)
-parenteral drug use	10(20)
-Sporadic or unknown	6(12)
Histology -no(%)	
-Chronic hepatitis	32(64)
-Cirrhosis	0(0)
-Unknown	18(36)
Serum HCV-RNA-mean value (X 10^5 eq/ml)	131.7
Serum ALT -mean value -[u/l(normal:10-50)]	127.4
Serum albumin-mean value -[g/dl(normal:3.5-5.5)]	4.2
Serum bilirubin-mean value -[mg/dl(normal:0.1-1.2)]	0.83
Leukocyte count -mean value -[$X10^3$/UL(normal:4.8-10.8)]	7.4
Status on enrollment-no (%)	
-Naive	41(82)
-interferon resistant	9(18)

Table-II. Pretreatment characteristics of the patients based upon Response to therapy with amantadine

Characteristic	Responder	Partial responder	Non responder
Age -years			
-Mean	34.2	43.7	48.0
-Range	(24-43)	(31-58)	(27-61)
Male sex -no (%)	6(21.43)	13(46.43)	9(32-14)
Source of infection - no (%)			
-Blood transfusion	9(18)	12(24)	13(26)
-Parenteral drug use	6(12)	3(6)	1(2)
-Sporadic or unknown	2(4)	3(6)	1(2)
Histology-no (%)			
-Chronic hepatitis	13(26)	9(18)	10(20)
-cirrhosis	0(0)	0(0)	0(0)
-unknown	4(8)	9(18)	5(10)
Serum HCV-RNA-mean value	31.4	123.6	191.8
-[$X10^5$ eq/ml(range)]	(10.5-49.2)	(43.2-221.9)	(29.4-241)
Serum ALT-mean value	84.4	156.7	124.3
-[U/L(range)]	(59-104)	(84-196)	(92-168)
Status on enrollment- no (%)			
-Naive	14(28)	16(32)	11(22)
-Interferon resistant	3(6)	2(4)	4(8)

DISCUSSION

In approximately 40% of patient with chronic hepatitis C, interferon therapy result in normalization of serum alanine amino transferase concentration , loss of detectable HCV-RNA in serum, and histology improvement, but the majority relapse shortly after treatment is stopped[4,5,6,10,11]. Many but not all of these patients have a responses are uncommon[12,13,14]. A second course of treatment with higher doses in than the first course or for longer period or both leads to sustained response in 20 to 50% of patient[12,13,15],but these regimens are costly and poorly tolerated.

The low magnitude of improvement with interferon and poor safety profile with escalated or extended therapy has led investigator to search for other drugs that may be effective in treatment of chronic hepatitis C.

The presents study provides evidence that amantadine and antiviral agent .has activity against hepatitis c virus. 17(34%) of 50 patients treated with amantadine for a period of six month, showed normalization in serum alanine aminotransferase concentrations and loss of HCV -RNA by PCR. No other antiviral agent has thus proved effectiveness as monotherapy when used in patients with hepatitis C . Other agents like ribavirin have been shown to decrease serum ALT levels but revealed no effect on HCV-RNA values. After cessation of therapy, even the observed biochemical response were noted to abate .In contrast, amantadine decreased serum ALT levels as well as HCV-RNA values, suggesting that the drug not only diminishes hepatic inflamation but also suppresses viral replication.

The likelihood of a favourable response to treatment with amantadine was related to the pretreatment serum HCV-RNA levels rather than ALT values. Patient with low serum HCV RNA titre had high w rates of response compared to those who did not respond to therapy . This efficacy was evident at the end of treatment as well as at the end of follow- up in terms of sustained normalization of alanine aminotransferase and sustained serum HCV-RNA

loss. The response rate was 26%for biochemical sustained response and 22% for virological sustained response.

Amantadine (1-amino adamantine hydrochloride) and other adamantine such as rimantadine were first shown to inhibit influenza A in the 1960s, yet few practitioners seem aware of their clinical potential. The antiviral mechanism of action has been shown to block events in late viral uncoating or early transcription[17]. The drug is almost completely absorbed when taken orally and is excreted unchanged in the urine. Peak plasma concentration are reached 1- 4 hours after ingestion of an oral dose of 2.5-5mg/kg. Amantadine is preferably concentrated in liver and this ability of getting high concentrations in liver along with its antiviral properties explains why amantadine may be effective in treatment of hepatitis C virus infection[7].

Therapy with amantadine was safe and reasonably well tolerated at the dose used in the present study with few side effects. Benefits of oral administration definitely improves patient's compliance and safety. Amantadine is considerably cost effective when compared to interferon.

The beneficial effect in this study also extended to those patient who have shown no response to interferon or left the treatment because of severe side effect of therapy. 3(33%) of 9 interferon non-responder patient cleared serum HCV-RNA by the end of treatment and 2 of those sustaining the response at six months follow- up. Both patient sustaining the response were previously intolerant to interferon therapy.

The safety profile based upon monthly symptom survey and clinical data showed no potential adverse events requiring dose modification or discontinuation of therapy. Minor neurological symptoms including insomnia light headedness, difficulty concentrating and headaches have been reported previously in 5-20% of patients receiving 200mg of amantadine daily[16]. Four patients complained of constipation and one patient presented with chest pain while on therapy. Although a cardiac source of chest pain was excluded in this case , amantadine should be used cautiously in patients with cardiovascular disorders as congestive cardiac failure has been associated with its use[17].

The present study was conducted both in the naive and interferon non- responder including those who did not tolerate the side effects of interferon and left the treatment. Amantadine has also been used successfully as monotherapy By J.P Smith[9] in a study of 22 patient who had previously failed standard therapy with interferon . 27% of patients in the study revealed normalization of ALT values and loss of HCV-RNA after six months while, 18% showed persistent clearance of HCV-RNA six months after termination of treatment . Since amantadine dose not depress leukocyte count or augment immunity, its use in patients with leucopaenia, autoimmune disease or organ transplants may also prove useful

The recommended prophylactic and therapeutic dose of amantadine in influenza A is 200 mg daily . The same regimen was opted against hepatitis C virus in this study for a period of six months, however the effect of extended therapy as well as the response to dose escalation should be assessed in patient with HCV infection who do not respond to the 200mg daily dose. Furthermore, additional trials using amantadine alone or in combination with other drug are required to establish the efficacy and durability of response, both in the naive and interferon resistant cases of hepatitis C.

CONCLUSION

As the result indicate Amantadine may be effective for treatment of patients with chronic hepatitis C who have not previously been treated- the naive cases - or have taken the treatment with interferon but left therapy due to intolerable side effects or no response. The improvement occurs not only in biochemical but also in virological markers of HCV infection suggesting the role of drug in reducing hepatic inflamation as well as suppressing viral replication . Amantadine has an acceptable safety profile and is

considerably economical as well. Thus ,the study show that therapy with amantadine is equally effective and safe in treatment of chronic hepatitis C. However , large multicentre, double blind, comparative clinical trials should be conducted to validate these findings and to make a proper worth of this safe and cost effective therapy.

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