

Comparative efficacy of Amantadine Hydrochloride versus Amantadine Sulphate in treating Egyptian patients with chronic HCV

Abstract

Background: Pegylated interferon (peg-IFN) alpha in combination with weight-based doses of ribavirin is currently recommended as a standard-of-care treatment for chronic hepatitis C virus (HCV) infection. However, the low response rate with interferon as well as the high occurrence of side effects, has prompted investigators to search for other drugs which may be efficacious in the treatment of hepatitis C.

Objectives: to evaluate the efficacy of amantadine hydrochloride versus amantadine sulphate monotherapy when administered to naïve Egyptian patients with chronic hepatitis C

Patients and Methods: Fifty Egyptian patients with chronic HCV were randomised with a ratio of 1:1 to receive amantadine hydrochloride (100mg) three times daily or amantadine sulphate (100mg) three times daily for sixty days .

Results : Patients treated with amantadine hydrochloride and amantadine sulphate showed highly significant reduction in serum AST and ALT levels but there was non significant reduction in HCV RNA viral load . Patients tolerate therapy well with no drop out.

Conclusions: amantadine oral therapy appears to have activity for treating hepatitis C

Key words: therapy, response, liver, transaminases, PCR

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28 Background

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30 Hepatitis C virus (HCV), which currently infects about 3% of the world's population (an
31 estimated 210 million people), is a major cause of chronic viral liver disease[1]. Chronic
32 hepatitis C is characterized by mostly mild hepatic inflammatory activity which does,
33 however, hold a significant risk of proceeding to liver cirrhosis and hepatocellular
34 carcinoma[2].

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36 Current gold-standard therapy for HCV infection is weekly subcutaneous injections of
37 pegylated interferon (PEG-IFN) combined with daily oral ribavirin for a period of 24
38 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4[3]. Therapy is fraught
39 with significant side effects that may cause discontinuation of therapy. Moreover,
40 therapy leads to a sustained virological response in approximately 40–50% of patients
41 with genotype 1 infection [4-8].

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43 The low response rate with interferon as well as the high occurrence of side effects has
44 prompted investigators to search for other drugs which may be efficacious in the
45 treatment of hepatitis C.

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In recent years, a favorable role of amantadine in the treatment of chronic hepatitis C has been suggested. Amantadine is a relatively inexpensive antiviral drug. It is a tricyclic amine, which was developed in the 1960s and registered in many countries for the prevention of influenza A infection and the treatment of Parkinson's disease [9]. Although the anti-viral mechanism of action of amantadine in chronic hepatitis C remains unclear, it may be related to the fact that amantadine can achieve high concentrations in the liver, [9] and may block events occurring in late viral uncoating or in early transcription. It may also be related to blockade of the p7 protein activity necessary for particle replication [10, 11]. So far, several clinical investigations in patients with chronic hepatitis C have shown that amantadine, when used as monotherapy, has no significant effect on the levels of HCV RNA, although a potential anti-inflammatory activity has been observed. [12-17]. Another small pilot study had shown that amantadine caused a response rate of about 18% in patients with hepatitis C who had previously failed interferon therapy [14]. So, the beneficial effects of amantadine monotherapy in hepatitis C virus infection have been reported in some [12,14,18], but not all [17] studies. The purpose of the present study was to evaluate the efficacy of amantadine hydrochloride versus amantadine sulphate monotherapy when administered to naïve Egyptian patients with chronic hepatitis C

Patients and Methods

Fifty chronic hepatitis C patients (32 females and 18 males) were included in the study. Patients' age ranged from 18 to 56 years. All patients gave their written informed consent

to participate in the clinical trial. The study protocol was approved by ethics committee and conformed to the ethical guide lines of the 1975.

Patients were randomized with a ratio of 1:1 to receive amantadine hydrochloride (adamine) 100mg, orally, three times daily for sixty days or amantadine sulphate (infex)100mg, orally , three times daily for sixty days

All patients were tested for HCV antibodies and Quantitative polymerase chain reaction (PCR) to measure HCV RNA viral load. Other laboratory tests included fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Bil T), serum albumin and complete bloodcount.

Statistical analysis

Analysis of the data was carried out using the Statistical Package for Science and Society (SPSS) (version 12, Chicago, Illinois, USA) software. Data were expressed as mean±standard deviation. Comparison between the mean values before and after treatment was performed using the paired Student's t-test. P values lower than 0.05 were considered statistically significant or highly significant, if <0.01) for all tests.

Results

The characteristics of the patients are shown in Table 1.

92 **Table 1. Baseline Characteristics of HCV Patients**

Lab	min	Max	Mean + SD
Age, y	18	56	35.89 ± 19.40
Body weight, Kg	56	98	69.87 ± 12.45
Blood glucose, mg/dL	90	403	165.54 ± 40.73
Bil T mg/dl	0.2	1.8	1.43 ± 0.89
AST, U/L	15	340	52.70 ± 31.21
ALT, U/L	12	280	64.03 ± 31.95
HCV load IU/ml	5450	1250000	18000.02 ± 1257.80

93 Bil T: Total bilirubin , AST: Aspartate aminotransferase , ALT; Alanine

94 aminotransferase, HCV: Hepatitis C virus

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96 Patients treated with amantadine hydrochloride showed highly significant reduction in
 97 serum AST and ALT levels (P value: 0.001) but there was none significant reduction in
 98 HCV RNA viral load (P value: 0.178) (Table 2).

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100 **Table 2 .Comparison between HCV load and liver enzymes before and after**
 101 **treatment with amantadine hydrochloride (group A)**

Lab	Mean±SD	Mean±SD	P value (significance)
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	Before	After	
HCV RNA	91575.9±23401.0	54083.8±16401.2	0.178
AST	49.6±6.7	13.7±4.3	0.001
ALT	57.8±7.1	12.8±4.8	0.001

AST: Aspartate aminotransferase , ALT; Alanine aminotransferase, HCV: Hepatitis C virus

Patients treated with amantadine sulphate showed highly significant reduction in serum AST and ALT levels (P value: 0.001) but there was none significant reduction in HCV RNA viral load (P value: 0.103)(Table 3).

Table3. Comparison between HCV load and liver enzymes before and after treatment with amantadine sulphate (group B)

Lab	Mean±SD	Mean±SD	P value
	Before	After	(significance)
HCV RNA	261664.8±154831.7	106119.5±101090.3	0.103
AST	45.3±7.5	16.9±3.7	0.001
ALT	50.0±2.1	16.6±3.8	0.001

AST: Aspartate aminotransferase , ALT; Alanine aminotransferase, HCV: Hepatitis C virus

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114 Discussion

115 The present study revealed that amantadine monotherapy induced a significant
116 biochemical response in Egyptian patients with chronic hepatitis C infection. Previous
117 studies supported the findings of our clinical trial in that amantadine therapy has antiviral
118 properties against hepatitis C [18, 19–21]. Tabone et al. studied the effects of 2 months
119 of amantadine monotherapy in 40 hepatitis C subjects and found a significant decline in
120 ALT levels without a response in HCV RNA [12]. Another study
121 [22] reported biochemical response after 3 months of amantadine therapy. In accordance
122 to our study, Martino et al. [22] found that this biochemical response was not associated
123 with a virological response. Senturk et al [23] treated twenty patients [in Turkey] with
124 amantadine HCl, 100 mg b.i.d., for 6 months. He observed biochemical improvement
125 without loss of HCV-RNA.

126 In spite of the small number of patients in this study, the decrease in serum ALT level
127 was highly significant. Such biochemical response is consistent with the findings of
128 previous reports [12, 14, 22].

129 A significant decrease in serum HCV RNA load was not observed in the present study.
130 This finding is consistent with the results of a previous study [12], although not with the
131 findings of Smith [14], who observed a sustained virological response in 18% of patients.
132 These discrepancies between biochemical and virological responses are supported by
133 recent experimental data [24]. However, this does not mean that amantadine therapy
134 could not be useful for chronic hepatitis C. Indeed, absence of a direct antiviral effect
135 also has been reported for treatment with ribavirin, which has been shown to decrease
136 both serum ALT level and liver necroinflammatory lesions when given alone [25] and to
137 improve sustained virological response when administered in combination with IFN [26].

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139 Forty two patients (96%) had concurrent medical disease such as severe hypertension,
140 heart failure, poorly controlled diabetes, chronic obstructive pulmonary disease.
141 Frequently, these patients are not candidates for interferon therapy [3]. A recent
142 study [27] found that of 293 hepatitis C–infected patients presenting for evaluation, 72%

were not eligible for interferon for reasons including noncompliance, medical contraindications, active substance abuse, patient preference. Perhaps amantadine may be useful in such patients.

Amantadine is an inexpensive and well tolerated drug. All patients in this study exhibited a favorable response to amantadine with excellent compliance, and zero percent dropout rate.

It had been shown that amantadine hydrochloride is comparable to amantadine sulphate as regards significant reduction in liver transaminases and non significant reduction in HCV RNA viral load.

In conclusion, amantadine oral therapy appears to have activity for treating hepatitis C. Certain populations that either do not respond to, or are intolerant of, interferon may be good candidates for amantadine monotherapy. Further studies are needed to evaluate higher doses and combination therapy with amantadine and other antiviral agents in Egyptian patients.

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