

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

Comment [a1]: Key words are not suitable words. The words of hepatitis C, treatment, Amantadine hydrochloride, Amantadine sulphate are better key words.

Background

Hepatitis C virus (HCV), which currently infects about 3% of the world's population (an estimated 210 million people), is a major cause of chronic viral liver disease [1,28]. Chronic hepatitis C is characterized by mostly mild hepatic inflammatory activity which does, however, hold a significant risk of proceeding to liver cirrhosis and hepatocellular carcinoma [2].

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

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.

Comment [a2]: • This percent is in world population, The author must be give us the prevalence of chronic C hepatitis between all of types of chronic hepatitis. As my previous survey in these patients, almost 21% of all chronic hepatitis was HCV Ab positive. (Monireh Rahimkhani, Hossein Khavari-Daneshvar and Sara Jamali. Serologic evaluation of hepatitis B and D in patients with cirrhosis. African Journal of Microbiology Research. 2011, Vol. 5(5) pp. 568-571.

Comment [a3]: Should be explain what is genotypes 1, 2 and 3?

UNDER PEER REVIEW

47 In recent years, a favorable role of amantadine in the treatment of chronic hepatitis C has
48 been suggested. Amantadine is a relatively inexpensive antiviral drug. It is a tricyclic
49 amine, which was developed in the 1960s and registered in many countries for the
50 prevention of influenza A infection and the treatment of Parkinson's disease [9]. Although
51 the anti-viral mechanism of action of amantadine in chronic hepatitis C remains unclear, it
52 may be related to the fact that amantadine can achieve high concentrations in the liver, [9]
53 and may block events occurring in late viral uncoating or in early transcription. It may
54 also be related to blockade of the p7 protein activity necessary for particle replication [10,
55 11]. So far, several clinical investigations in patients with chronic hepatitis C have shown
56 that amantadine, when used as monotherapy, has no significant effect on the levels of
57 HCV RNA, although a potential anti-inflammatory activity has been observed. [12-17].
58 Another small pilot study had shown that amantadine caused a response rate of about 18%
59 in patients with hepatitis C who had previously failed interferon therapy [14]. So, the
60 beneficial effects of amantadine monotherapy in hepatitis C virus infection have been
61 reported in some [12,14,18], but not all [17] studies. The purpose of the present study was
62 to evaluate the efficacy of amantadine hydrochloride versus amantadine sulphate
63 monotherapy when administered to naïve Egyptian patients with chronic hepatitis C

64

65 Patients and Methods

66

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

UNDER PEER REVIEW

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

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

74 All patients were tested for HCV antibodies and Quantitative polymerase chain reaction
75 (PCR) to measure HCV RNA viral load. Other laboratory tests included fasting blood

76 glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total
77 bilirubin (Bil T), serum albumin and complete bloodcount.

78

79 Statistical analysis

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

85

86 Results

87

88 The characteristics of the patients are shown in Table 1.

89

90

91

Comment [a4]: Why author measured the FBS? What is the related to chronic hepatitis?

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

95

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).

99

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)
-----	---------	---------	---------------------------

	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

Comment [a5]: In chronic hepatitis AST and ALT were not much high level so the measuring of these enzymes is not good markers for following of treatment chronic hepatitis. The gold reason for treatment of chronic hepatitis is reduction genome of HCV.

113

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 of
 119 amantadine monotherapy in 40 hepatitis C subjects and found a significant decline in ALT
 120 levels without a response in HCV RNA [12]. Another study [22] reported biochemical
 121 response after 3 months of amantadine therapy. In accordance to our study, Martino et al.
 122 [22] found that this biochemical response was not associated with a virological response.
 123 Senturk et al [23] treated twenty patients [in Turkey] with amantadine HCl, 100 mg b.i.d.,
 124 for 6 months. He observed biochemical improvement without loss of HCV-RNA.
 125 In spite of the small number of patients in this study, the decrease in serum ALT level
 126 was highly significant. Such biochemical response is consistent with the findings of
 127 previous reports [12,14, 22].
 128 A significant decrease in serum HCV RNA load was not observed in the present study.
 129 This finding is consistent with the results of a previous study [12], although not with the
 130 findings of Smith [14], who observed a sustained virological response in 18% of patients.
 131 These discrepancies between biochemical and virological responses are supported by
 132 recent experimental data [24]. However, this does not mean that amantadine therapy
 133 could not be useful for chronic hepatitis C. Indeed, absence of a direct antiviral effect also
 134 has been reported for treatment with ribavirin, which has been shown to decrease both
 135 serum ALT level and liver necroinflammatory lesions when given alone [25] and to
 136 improve sustained virological response when administered in combination with IFN [26].
 137
 138 Forty two patients (96%) had concurrent medical disease such as severe hypertension,
 139 heart failure, poorly controlled diabetes, chronic obstructive pulmonary disease.
 140 Frequently, these patients are not candidates for interferon therapy [3]. A recent
 141 study [27] found that of 293 hepatitis C–infected patients presenting for evaluation, 72%
 142

UNDER PEER REVIEW

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.

References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005;5:558-567.
2. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36: S35-S46
3. Ghany MG, Strader DB, Thomas DL, Ghany MG, Strader DB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; 49: 1335-74.

UNDER PEER REVIEW

- 174 4. Manns MP, McHutchinson JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al.
175 Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for
176 initial treatment of chronic hepatitis C. a randomized trial. *Lancet* 2001; 358:958–65.
177
- 178 5. McHutchinson JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al.
179 Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic
180 hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339:1485–92.
181
- 182 6. Poynard T, McHutchinson J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact
183 of pegylated interferon α -2b and ribavirin on liver fibrosis in patients with chronic
184 hepatitis C. *Gastroenterology* 2002; 122:1303–13.
185
- 186 7. Sarasin-Filipowicz M. Interferon therapy of hepatitis C: molecular insights into
187 success and failure. *Swiss Med Wkly.* 2009;140:3–11.
188
- 189 8. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al.
190 Peginterferon α -2a in patients with chronic hepatitis C. *N Engl J Med* 2000; 343:1666–72.
191
- 192 9. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride.
193 *Clin Pharmacol* 1988; 14: 35–51.
194
- 195 10. Griffin SDC, Beales LP, Clarke DS, Worsfold O, Evans SD, Jaeger J, et al. The p7
196 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug,
197 amantadine. *FEBS Lett.* 2003;535:34–8.
198
- 199 11. Skehel JJ, Hay AJ, Armstrong JA. On the mechanism of inhibition of influenzae virus
200 replication by amantadine hydrochloride. *J Gen Virol* 1978; 38: 97–110.
201
- 202 12. Andant C, Lamoril J, Deybach JC, Jouet P, Soule JC. Amantadine for chronic
203 hepatitis C: a pilot study in 14 patients. *Eur J Gastroenterol Hepatol* 2000; 12: 1319–22.
204

UNDER PEER REVIEW

13. Cozzolongo R, Cuppone R, Manghisi OG. The treatment of chronic hepatitis C not responding to interferon. *Curr Pharm Des.* 2002;8(11):967-75. Review.
14. Senturk H, Mert A, Akdogan M, Tabak F, Basaran G, Turkoglu S, et al. Amantadine monotherapy of chronic hepatitis C in patients infected with genotype 1b. *Scand J Infect Dis* 2000; 32: 575–6.
15. Smith JP. Treatment of chronic hepatitis C with amantadine. *Dig Dis Sci* 1997; 42: 1681–7.
16. Tabone M, Ercole E, Zaffino C, Sallio Bruno F, Pera A, Bonino F. Amantadine hydrochloride decreases serum ALT activity without effects on serum HCV-RNA in chronic hepatitis C patients. *Ital J GastroenterolHepatol* 1998; 30: 611–3.
17. Yagura M, Harada H. Treatment of chronic hepatitis C patients with amantadine. *J Gastroenterol* 2001; 36: 759–63.
18. Adinolfi LE, Utili R, Tonziello A, Ruggiero G. Effects of alpha interferon induction plus ribavirin with or without amantadine in the treatment of interferon non-responsive chronic hepatitis C: a randomized trial. *Gut.* 2003;52:701–5.
19. Berg T, Kronenberger B, Hinrichsen H, Gerlach T, Buggisch P, Herrmann E, et al. Triple therapy with amantadine in treatment-naive patients with chronic hepatitis C: a placebo-controlled trial. *Hepatology.* 2003;37:1359–67.
20. Mangia A, Minerva N, Annese M, Leandro G, Villani MR, Santoro R, et al. A randomized trial of amantadine and interferon versus interferon alone as initial treatment for chronic hepatitis C. *Hepatology* 2001; 33: 989– 93.

UNDER PEER REVIEW

- 234 21. Zeuzem S, Teuber G, Naumann U, Berg T, Raedle J, Hartmann S, et al. Randomized,
235 double-blind, placebo-controlled trial of interferon alfa 2a with and without amantadine
236 as initial treatment for chronic hepatitis C. *Hepatology*. 2000;32:835–41.
237
- 238 22. Martino VD, Boudjema H, Delacour T, Cazier A, Caron C, Coutarel P, et al.
239 Treatment of Chronic Hepatitis C with Amantadine Hydrochloride in Patients Who Had
240 Not Responded to Previous Treatment with Interferon- α and/or Ribavirin. *Clinical*
241 *Infectious Diseases* 2001; 32(5):830–1
242
- 243 24. Jubin R, Murray MG, Howe AY, Butkiewicz N, Hong Z, Lau JY. Amantadine and
244 rimantadine have no direct inhibitory effects against hepatitis C viral protease, helicase,
245 ATPase, polymerase, and internal ribosomal entry site-mediated translation. *J Infect Dis*
246 2000; 181:331-4.
247
- 248 25. Zoulim F, Haem J, Ahmed SS, Chossegros P, Habersetzer F, Chevallier M, et al.
249 Ribavirin monotherapy in patients with chronic hepatitis C: a retrospective study of 95
250 patients. *J Viral Hepat* 1998;5:193-8.
251
- 252 26. Hadziyannis SJ, Sette HJ, Morgan TR, Balan V, Diago M, Marcellin P, et al.
253 Peginterferon- α 2a and ribavirin combination therapy in chronic hepatitis C: a
254 randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:
255 346-355.
256
- 257 27. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ.
258 Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern*
259 *Med*. 2002; 136(4):288-92
260
- 261 28- Monireh Rahimkhani, Hossein Khavari-Daneshvar and Sara Jamali. Serologic
262 evaluation of hepatitis B and D in patients with cirrhosis. *African Journal of*
Microbiology Research. 2011, Vol. 5(5) pp. 568-571.