

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 randomized to receive amantadine hydrochloride (100mg) two times daily or amantadine sulphate (100mg) two 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: hepatitis C, treatment, Amantadine hydrochloride, Amantadine sulphate

Background

Almost 21% of all patients with chronic hepatitis proved to be HCV Ab positive

[1]. 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].

First and second generation of protease and polymerase inhibitors (telaprevir, boceprevir, sofosbuvir, simaprevir) are used for treatment of HCV in West Europe and USA. In developing countries, pegylated interferon (PEG-IFN) combined with daily oral ribavirin is used [3]. However, interferon based 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 [4-8].

The low response rate with pegylated 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.

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 level of HCV RNA, although a potential anti-inflammatory activity has been observed. [12-17]. Another small pilot study had shown that amantadine cause 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 which was conducted in the General Transport Authority in the period between November 2012 to March 2014. They were selected from 180 patients. Only patients with contraindication to Peg-IFN/RBV therapy were included. Seventy percent of the included patients were suffering from chronic obstructive pulmonary disease while thirty percent were suffering from poorly controlled diabetes. 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 equal distribution to 2 treatment regimens using block of 6 and randomization envelopes were prepared by the biostatistician. This study was open label; therefore no blinding procedures were required.

Twenty five patients received amantadine hydrochloride (adamine) 100mg, orally, two times daily for sixty days and 25 patients received amantadine sulphate (infex)100mg, orally , two times daily for sixty days.

Before starting treatment, all patients were tested for HCV RNA viral load by real time polymerase chain reaction (PCR) (Applied biosystems). Other laboratory tests included fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Bil T), serum albumin and complete blood count. Six months after treatment, serum transaminases and HCV RNA viral load were re- evaluated.

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 $\pm$ 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.

Table 1. Baseline Characteristics of HCV Patients

Lab	min	Max	Mean + SD
Age, years	18	56	35.89 $\pm$ 19.40
BMI	27	49	47.5 $\pm$ 5.2
Blood glucose, mg/dL	90	403	165.54 $\pm$ 40.73
Bil T mg/dl	0.2	1.8	1.43 $\pm$ 0.89
AST, U/L	15	340	52.70 $\pm$ 31.21
ALT, U/L	12	280	64.03 $\pm$ 31.95
HCV load IU/ml	5450	1250000	18000.02 $\pm$ 1257.80

BMI: Body mass index, Bil T: Total bilirubin , AST: Aspartate aminotransferase , ALT; Alanine aminotransferase, HCV: Hepatitis C virus

Patients treated with amantadine hydrochloride showed highly significant reduction in serum AST and ALT levels (P value: 0.001) but there was non significant reduction in HCV RNA viral load (P value: 0.178) (Table 2).

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

Lab	Mean $\pm$ SD Before	Mean $\pm$ SD After	P value (significance)
HCV RNA	91575.9 $\pm$ 23401.0	54083.8 $\pm$ 16401.2	0.178
AST	49.6 $\pm$ 6.7	13.7 $\pm$ 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 non 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 Before	Mean±SD After	P value (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

Discussion

The present study revealed that amantadine monotherapy induced a significant biochemical response in Egyptian patients with chronic hepatitis C infection. Previous studies supported the findings of our clinical trial in that amantadine therapy has antiviral properties against hepatitis C [18, 19–21]. Palabıyıkoglu et al. [12] treated 22 patients with past history of non response to peg. INF/ RBV therapy with amantadine (200mg/day) daily for at least 24 weeks (mean 96 weeks) and HCV-RNA was assessed every 12 weeks starting from the 24th week, without discontinuation of therapy. They found that, 1 patient became HCV-RNA negative at the 24th and 3 patients at the 48th week (response rate at week 48 was 18.2%), 1 patient at the second year and 1 patient at the fourth year of the treatment (p=0.031). However, Martino et al. [22] found that biochemical response was not associated with a virological response. In accordance to

our study, Senturk et al [23] treated twenty patients [in Turkey] with amantadine HCl, 100 mg b.i.d., for 6 months. He observed biochemical improvement without loss of HCV-RNA.

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

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

A study found that of 293 hepatitis C–infected patients presenting for evaluation, 72% were not eligible for interferon based therapy for reasons including noncompliance, medical contraindications, active substance abuse, patient preference [27]. Perhaps amantadine may be useful in such patients especially in developing countries lacking directly acting antivirals.

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. Patients in both groups showed minimal side effects.

In conclusion, amantadine oral therapy appears to have activity for treating hepatitis C. Amantadine hydrochloride and amantadine sulphate show similar results regarding significant reduction in liver enzymes and insignificant reduction in HCV load. Because directly acting antiviral drugs are very expensive and not available in most developing countries it is advisable to search for alternative solutions to bridge the time till that drugs should be available. One alternative could be amantadine in patients with contraindications for Interferon –based therapy and in relapsers or non responders to standard therapy (like UDCA- ursodesoxycholic acid- lowering aminotranspherase levels without effect on HCV RNA). Further studies are needed to evaluate higher doses and combination therapy with amantadine and directly acting antiviral drugs in Egyptian patients.

Acknowledgment

I would like to thank the reviewers for their valuable comments.

References

1. Rahimkhani M, Khavari-Daneshvar H and Jamali S. Serologic evaluation of hepatitis B and D in patients with cirrhosis. African Journal of Microbiology Research 2011; 5(5): 568-571.
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.
4. Manns MP, McHutchinson JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C. a randomized trial. Lancet 2001; 358:958–65.

199

200 5. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al.
201 Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic
202 hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998; 339:1485–92.

203

204 6. Poynard T, McHutchinson J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact
205 of pegylated interferon α -2b and ribavirin on liver fibrosis in patients with chronic
206 hepatitis C. Gastroenterology 2002; 122:1303–13.

207

208 7. Sarasin-Filipowicz M. Interferon therapy of hepatitis C: molecular insights into
209 success and failure. Swiss Med Wkly. 2009;140:3–11.

210

211 8. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al.
212 Peginterferon α -2a inpatients with chronic hepatitis C. N Engl J Med 2000; 343:1666–72.

213

214 9. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride.
215 ClinPharmacol 1988; 14: 35–51.

216

217 10. Griffin SDC, Beales LP, Clarke DS, Worsfold O, Evans SD, Jaeger J, et al. The p7
218 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug,
219 amantadine. FEBS Lett. 2003;535:34–8.

220

221 11. Skehel JJ, Hay AJ, Armstrong JA. On the mechanism of inhibition of influenzae virus
222 replication by amantadine hydrochloride. J Gen Virol 1978; 38: 97–110.

223

224 12. Palabıyıkoglu M, Ormeci N, Ekiz F, Beyler AR, Erdem H, Dökmeci A, et al.
225 Amantadine in non-responder patients with chronic hepatitis C: a randomized prospective
226 study. Hepatogastroenterology. 2012;59(118):1911-4.

227

228 13. Cozzolongo R, Cuppone R, Manghisi OG. The treatment of chronic hepatitis C not
229 responding to interferon. Curr Pharm Des. 2002; 8(11):967-75. Review.

- 230
- 231 14. Smith JP. Treatment of chronic hepatitis C with amantadine. *Dig Dis Sci*. 1997;
232 42(8):1681-7.
- 233
- 234 15. Steinmann E1, Whitfield T, Kallis S, Dwek RA, Zitzmann N, Pietschmann T, et al.
235 Antiviral effects of amantadine and iminosugar derivatives against hepatitis C virus.
236 *Hepatology* 2007; 46(2):330-8.
- 237
- 238 16. Castelain S, Bonte D, Penin F, François C, Capron D, Dedeurwaerder S, et al.
239 Hepatitis C Virus p7 membrane protein quasispecies variability in chronically infected
240 patients treated with interferon and ribavirin, with or without amantadine. *J Med Virol*.
241 2007; 79(2):144-54.
- 242
- 243 17. Khokhar N, Qureshi MO, Niazi TK. Treatment of decompensated cirrhosis secondary
244 to hepatitis C with antiviral therapy. *J Coll Physicians Surg Pak*. 2013; 23(12):833-6.
- 245
- 246 18. Adinolfi LE, Utili R, Tonziello A, Ruggiero G. Effects of alpha interferon induction
247 plus ribavirin with or without amantadine in the treatment of interferon non-responsive
248 chronic hepatitis C: a randomized trial. *Gut*. 2003;52:701-5.
- 249
- 250 19. Berg T, Kronenberger B, Hinrichsen H, Gerlach T, Buggisch P, Herrmann E, et al.
251 Triple therapy with amantadine in treatment-naïve patients with chronic hepatitis C: a
252 placebo-controlled trial. *Hepatology*. 2003;37:1359-67.
- 253
- 254 20. Mangia A, Minerva N, Annese M, Leandro G, Villani MR, Santoro R, et al. A
255 randomized trial of amantadine and interferon versus interferon alone as initial treatment
256 for chronic hepatitis C. *Hepatology* 2001; 33: 989- 93.
- 257
- 258 21. Zeuzem S, Teuber G, Naumann U, Berg T, Raedle J, Hartmann S, et al. Randomized,
259 double-blind, placebo-controlled trial of interferon alfa 2a with and without amantadine
260 as initial treatment for chronic hepatitis C. *Hepatology*. 2000;32:835-41.

22. Martino VD, Boudjema H, Delacour T, Cazier A, Caron C, Coutarel P, et al. Treatment of Chronic Hepatitis C with Amantadine Hydrochloride in Patients Who Had Not Responded to Previous Treatment with Interferon-a and/or Ribavirin. *Clinical Infectious Diseases* 2001; 32(5):830–1
23. Senturk H, Mert A, Akdogan M, Tabak F, Basaran G, Turkoglu S, et al. Amantadine monotherapy of chronic hepatitis C patients infected with genotype 1b. *Scand J Infect Dis.* 2000;32(5):575-6.
24. Jubin R, Murray MG, Howe AY, Butkiewicz N, Hong Z, Lau JY. Amantadine and rimantadine have no direct inhibitory effects against hepatitis C viral protease, helicase, ATPase, polymerase, and internal ribosomal entry site-mediated translation. *J Infect Dis* 2000; 181:331-4.
25. Zoulim F, Haem J, Ahmed SS, Chossegros P, Habersetzer F, Chevallier M, et al. Ribavirin monotherapy in patients with chronic hepatitis C: a retrospective study of 95 patients. *J Viral Hepat* 1998;5:193-8.
26. Hadziyannis SJ, Sette HJ, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346-355.
27. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med.* 2002; 136(4):288-92