COMMENTED ARTICLES

Amantadine therapy for chronic hepatitis C: a dose escalation study

Am J Gastroenterol 2004 Jun; 99(6):1099-104.

Smith JP, Riley TR 3rd , Bingaman S, Mauger DT.

OBJECTIVES: Amantadine reduces liver transaminase levels in some patients with chronic hepatitis C at doses of 200 mg daily and may improve the sustained virological response (SVR) when given with interferon and ribavirin. The primary purpose of the present investigation was to study the safety and toxicity of higher doses of amantadine in subjects who previously failed or were intolerant to interferon. The secondary aim was to test the efficacy of higher dose of amantadine against hepatitis C.

METHODS: An open-labeled prospective study was conducted starting with amantadine 200 mg daily and increasing to 500 mg daily while monitoring for safety, toxicity, and efficacy. An amantadine blood level exceeding 1,600 ng/ml was considered toxic requiring dose reduction. The patient's symptoms, laboratory tests, and quality of life were monitored.

RESULTS: One hundred patients enrolled in the study. Normalization of alanine aminotransferase (ALT) for each dose was as follows: 200 mg (35%), 300 mg (49%), 400 mg (53%), and 500 mg (56%). The incidence of toxic amantadine plasma levels increased with dose, i.e., 200 mg (0%), 300 mg (6%), 400 mg (27%), and 500 mg (49%). The frequency and severity of arthralgia and fatigue improved at all dosages administered. No changes in the occurrence or severity of headache, insomnia, or depression were reported. Serious adverse events included myocardial infarction and suicide attempt. Other side effects included impotence, confusion, alopecia, and hoarseness.

CONCLUSIONS: Amantadine given at a dose of 300 mg daily is safe, and significantly lowers ALT blood levels more than 200 mg daily. The enzyme response rate does not significantly improve above 300 mg, but toxicity increases.

Hepatitis Monthly Editorial Board Comment

The Amantadine story in the treatment of HCV:a moving pendulum

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Amantadine (AMA) is an effective antiviral in the prevention of influenza A.[1] In early 1990s reports showed its potential benefit in the treatment of hepatitis C[2, 3] , but the AMA's mechanism of antiviral action in HCV is still unclear.[2] In 1997 several studies suggested the combination of Interferon alfa (IFN alfa) and AMA for treatment of HCV [4, 5] , but in the subsequent years Khalili et al. demonstrated the lack of efficacy of dual therapy with interferon and AMA for interferon nonresponders [6] and in conjunction with the majority of abstracts presented at the Digestive Disease Week (DDW) 2000, it was confirmed that there was no role for dual therapy with IFN alfa /AMA in the treatment of hepatitis C, both in IFN alfa nonresponders and naive patients.[7-9] The storyTwas temporarily abundant while

Mangia et al, in a well designed multicenter randomized study showed the superiority of IFN alfa and AMA combination over IFN alfa monotherapy.[10] So the pendulum moved again to the opposite side, and the pendulum continued swinging till Mangia et al, in a recent meta-analysis showed that therapy with AMA and IFN alfa is effective and may be an alternative to IFN alfa and ribavirin (RBV) in patients who cannot tolerate RBV.[11] All the studies discussed above used the usual anti-influenza dose of 200 mg/d of AMA but the current study of Smith JP[12] was the first toxicologic and dose escalation study upon AMA which showed that 300 mg/d is well tolerated and lowers ALT more than 200 mg/d. This makes one eager of knowing the efficacy of the AMA 300 mg/d in combination with IFN alfa in future studies. Looking from another point of view, triple therapy of AMA, IFN alfa and RBV has recently been shown to be effective in IFN alfa plus RBV nonresponders.[13, 14] In summary, after several swings of the AMA pendulum during the last 10 years it seems that at present AMA has a lot to say with 300 mg daily dose in combination with IFN alfa ± RBV specially for a group of HCV infected patients unresponsive to standard IFN alfa plus RBV treatment or those with hemoglobolinopathies in whom RBV is contraindicated.

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