

Correlation between hepatitis C serostatus and methadone dose requirement in 1,163 methadone-maintained patients

Sarz Maxwell, Marc S. Shinderman, Alicia Miner, Annette Bennet

Summary

Hepatitis C infection is epidemic in intravenous drug users worldwide. This has great impact on opiate-addicted patients. Prevention of infection must depend on treatment of opiate addiction. This report discusses findings from 1,163 methadone-maintained patients tested for hepatitis C infection. The prevalence of HCV seropositivity in IVDU patients was 68%. Seropositive patients required significantly higher doses of methadone (169 mg/d vs. 100 mg/d, $p < .05$). This difference in dose was independent of duration of addiction and time in treatment. It is suggested that Hepatitis C infection may be associated with metabolic changes that lead to increased methadone requirement.

Key words: Methadone Maintenance - Methadone Dose -
Hepatitis C Infection

Introduction

Hepatitis C infection is increasingly recognized as a world health problem. The most important vector of infection is intravenous drug use (IVDU), and the prevalence of hepatitis C virus (HCV) infection in patients with a history of IVDU averages 75-90%. This infection prevalence is fairly consistent worldwide [2,5,8,11,16].

Though antiviral treatment regimens can be efficacious in the treatment of HCV infection, the most effective intervention is prevention. For prevention of HCV infection, measures must be targeted against intravenous drug use, the most common cause of HCV infection. The most effective method of preventing intravenous drug use is addiction treatment, and the most effective treatment for opioid addiction (the drug most commonly used intravenously) is methadone maintenance treatment (MMT) [6,14,20]. In this study we report epidemiologic trends in 1,163 MMT patients tested for

HCV, and discuss clinical associations between HCV seropositivity and increased methadone dose requirement.

Method

All patients were enrolled for MMT at Center for Addictive Problems (CAP), a private clinic in a central urban location. The average census at CAP is approximately 1,150 patients, and the mean methadone dose is approximately 130 mg/d. Between 1995 and 1999, most patients tested for HCV-Ab were those identified by counselor or physician as being at high risk for HCV infection, with the most important risk factor being IVDU history. Prior to October 1999, patients could have HCV-Ab testing done through our facility by getting a laboratory requisition from the physician, undergoing phlebotomy during the hours that a phlebotomist was available at the clinic (approximately 6 hours/week), and paying the laboratory fee. The assay used was Abbott HCV antibody enzyme immunoassay. Between October 1999 and January 2001 we were able to offer free and less invasive (fingerstick rather than venipuncture) HCV-Ab testing routinely to all patients, including all new admissions. Counsellors performed HCV education with all patients and actively recommended testing, particularly to patients with significant risk factors for HCV infection. These free tests were offered via Home Access, and the assay used was Ortho HCV Version 3.0 ELISA, with positive results confirmed by repeat ELISA and CHIRON RIBA HCV 3.0 SIA. A database had been maintained by the authors since early 1999, cataloguing clinical and epidemiologic data for all patients tested. Risk factors were determined by patient self-report in a standardized form administered at time of testing. History of cocaine use was determined by patient report and urine toxicology results. Urine toxicology results discussed here are the most recent done for each patient. Correlations between categorical variables were assessed using the chi-square statistic; correlations between quantitative variables were assessed by t-test.

Results

Of the 1,201 patients who underwent HCV-Ab testing, 38 (3%) were excluded from analysis because their test results were indeterminate even after repeated testing. The remaining study group consisted of 1,163 patients, of whom 387 (33%) were female. History of IVDU was reported in 694 (59.7%). Of these IVDU patients, 470 (68%) tested HCV+, and 224 (32%) were HCV-; this correlation was significant at the $p < .05$ level ($r = 0.50$). HCV status also correlated with mean years of addiction (21.3 years for HCV+ patients versus 9.3 years for HCV- patients, $r = 0.55$, $p < .05$) and with mean months in treatment (65.0 months versus 25.9 months, $r = 0.35$, $p < .05$). Both of these findings were consistent with the difference in mean age between groups (44.4 years versus 33.8 years, $r = 0.50$, $p < .05$). While the differences were modest, HCV+ patients were more likely to be female ($r = 0.50$, $p < .05$) and Caucasian ($r = 0.17$, $p < .05$). HCV+

patients were taking significantly higher doses of methadone: 169 mg/day versus 100 mg/day ($r=0.27$, $p<.05$). The relationship between HCV status and methadone dose remained statistically significant in partial correlations that controlled for mean years since addiction ($r=0.15$, $p<.05$) and for mean months in treatment ($r=0.22$, $p<.05$).

Discussion

In our population 85.5% of patients who report any history of IVDU are HCV+, a prevalence consistent with the world literature. Our population is also in agreement with the world literature regarding demographic and risk factors. The HCV+ patients tend to be older than HCV-patients (44.4 years vs. 33.8 years) and to have longer addiction histories (21.3 yr vs. 9.3 yr). In our clinic this means that the majority of HCV+ patients have been stable in treatment for years before learning of their HCV infection. This is consistent with the course of HCV infection, which may remain dormant and asymptomatic for 15-20 years [19].

In our sample, women are over-represented in the HCV+ group; other researchers have reported this [17], and a Chicago group has suggested the influence of sexual transmission accounting for this [8]: as with HIV infection, sexual transmission may be more efficient in the infection of female patients. The ethnic demography seems to run contrary to HIV infection, however; in our sample there is a predominance of Caucasian patients.

The yield from screening for HCV infection can be improved significantly by screening first for risk factors, particularly history (even, perhaps especially, remote history) of intravenous drug use. In a Yale analysis of screening algorithms, age, IVDU, and history of hepatitis correlated with HCV infection at the $p<.001$ level [9]. Measurement of liver function tests is a very insensitive screen; at least of infected patients have normal transaminase levels [1, 22].

MMT is the most effective treatment for opiate addiction, and should be effective prevention for HCV seroconversion, but studies of HCV seroconversion in patients enrolled in MMT [4, 13, 21] have been discouraging. One Australian study reported seroconversion as frequently in MMT patients as those out of treatment [4]. However, in this study the average methadone dose was only 42 mg/d, indicating that the majority of patients in that clinic were being medicated at doses far below those generally recommended. Indeed, 93% of patients in that MMT programme were still using heroin. Many clinics reporting poor efficacy of MMT in preventing new HCV infections did not report the dose of methadone prescribed, and may well have also been using subtherapeutic doses. Dose of methadone is directly related to efficacy of MMT in eradicating illicit opioid use [3, 7, 15, 18].

Unfortunately, the majority of MMT clinics in the United States use inadequate doses of methadone, resulting in high rates of continued illicit opioid use [20]. We have previously reported that the range of doses required to adequately treat opioid addicts may be wider than previously suspected. In our 1999 study we reported patients treated with doses in the range of 120 - 780 mg/d (10); since then we have had experience with

several patients requiring >1000 mg/d of methadone.

In the mid-1990's we noticed a clinical trend that interested us enough to being keeping a database about HCV infection. Long-term patients, stable and illicit-drug-free for years or even decades, presented complaining that the methadone dose that had kept them stable for years had stopped "holding" them. Many were impelled to buy illicit methadone in order to prevent opiate abstinence syndrome while continuing to avoid heroin use. As we titrated these patients' methadone dose against symptoms of opiate abstinence syndrome (OAS), we found that the increases in dose requirement were significant and in some cases startling: up to 10-fold. As HCV-Ab testing became readily available, we noticed that this dose phenomenon was happening in the same long-term, older patients that were testing positive for HCV-Ab.

This large analysis proves a significant correlation between HCV+ and methadone dose. Other clinicians in Europe have noted this correlation [12]. Correlation does not automatically confer causality, and we explored other possible factors involved in this population requiring higher doses, particularly time in treatment. Our analyses showed that the correlation between higher dose and HCV+ status was independent of the patient's age, length of opioid addiction, and time in treatment. It is tempting to speculate that HCV has specific effects on hepatic function, and these clinical observations suggest a unique effect.

Whereas most other hepatidites impair the activity of the Cytochrome P450 enzyme system, our clinical observations are more consistent with a cytochrome induction phenomenon. This possibility deserves further study, as it could have significant impact on the treatment of HCV and related conditions.

References

1. Bell J., Batey R. G., Farrel G. C., Crewe E. B., Cunningham A. L., Byrth K. (1990): Hepatitis C virus in intravenous drug users. *Med J Aust.* 153(5): 274-276.
2. Bolumar F., Hernandez-Aguado I., Ferrer L., Ruiz I., Avino M. J., Rebagliato M. (1996): Prevalence of antibodies to hepatitis C in a population of intravenous drug users in Valencia, Spain, 1990-1992. *Int J. Epidemiol.* 25(1): 204-209.
3. Caplehorn J. R. M., Bell J. (1991): Methadone dosage and retention of patients in maintenance treatment. *Med J Aust.* 154: 195-199.
4. Crofts N., Nigro L., Ornan K., Stevenson E., Sherman J. (1997): Methadone maintenance and hepatitis C virus infection among injecting users. *Addiction.* 92(8): 999-1005.
5. Galeazzi B., Tufano A., Barbierato E., Bortolotti F. (1995): Hepatitis C infection in Italian intravenous drug users: epidemiological and clinical aspects. *Liver.* 15(4): 209-212.
6. Goldstein A. (1991): Heroin addiction: neurobiology, pharmacology, and policy. *J Psychoactive Drugs.* 23(2): 123-133.
7. Hartel D. M., Schoenbaum E. E., Selwyn P. A., Kline J., Davenny K., Klein R. S., Friedland G. H. (1995): Heroin use during methadone maintenance treatment: the

- importance of methadone dose and cocaine use. *Am J Public Health*. 85(1): 83-88.
8. Hershow R. C., Kalish L. A., Sha B., Till M., Cohen M. (1998): Hepatitis C virus infection in Chicago women with or at risk for HIV infection: evidence for sexual transmission. *Sex Trasm Dis*. 25(10): 527-532.
 9. Magriples U., Bernstein P., Snyder E., Coipel J. A. (1998): Can risk factor screening predict hepatitis C antibody reactivity? *Am J Perinatol*. 15(6): 395-398.
 10. Maxwell S., Shinderman M. (1999): Optimizing Response to Methadone Maintenance Treatment: Use of Higher-Dose Methadone. *J Psychoactive Drugs*. 31(2): 95-102.
 11. Neuwald C. V., Pont J., Tomasits J., Bauer K. (1992): Antibody prevalence for hepatitis C and other parenterally transmissible viral diseases in drug dependent patients. *Acta Med Austriaca*. 19(2): 47-48.
 12. Okruhlica L., Klempova D. (2000): Hepatitis C infected patients and higher doses of methadone [Letter]. *Heroin Add & Rel Clin Probl*. 2(2): 57-58.
 13. Selvey L. A., Denton M., Plant A. J. (1997): Incidence and prevalence of hepatitis C among clients of a Brisbane methadone clinic: factors influencing hepatitis C serostatus. *Austr N Z J Public Health*. 21(1): 102-104.
 14. Senay E. C. (1985): Methadone maintenance treatment. *Int J Addict*. 20(6-7): 803-821.
 15. Siassi I., Angle B. P., Alston D. C. (1977): Comparison of the effect of high and low doses of methadone on treatment outcome. *Int J Addict*. 12(8): 993-1005.
 16. Sinniah M., Ooi B. G. (1993): Hepatitis C – the Malaysian story. *Singapore Med J*. 34(2): 132-134.
 17. Smyth R., Keenan E., Dorman A., O'Connor J. (1995): Hepatitis C infection among injecting drug users attending the National Drug Treatment Centre. *Ir J Med Sci*. 164(4): 267-268.
 18. Strain E. C., Stitzer M. L., Liebson I. A., Bigelow G. E. (1993): Methadone dose and treatment outcome. *Drug Alcohol Depend*. 33(2): 105-117.
 19. Tong M. J., el-Farra N. S. (1996): Clinical sequelae of hepatitis C from injection drug use. *West J Med*. 164(5): 399-404.
 20. United States Genral Accounting Office (1990): *Methadone maintenance: some treatment programs are not effective; greater deferral oversight needed*, GAO/HRD.
 21. Van Beek I., Dwyer R., Dore G. J., Kaldor J. M. (1998): Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *Br Med J*. 317(7156): 433-437.
 22. Van Thiel D. H., Caraceni P., Molloy P. J., Hassanein T., Kania R. J., Gurakar A., Friedlander L. (1995): Chronic hepatitis C in patients with normal or near normal alanine aminotransferase levels: the role of interferon alpha 2b therapy. *J Hepatol*. 23(5): 503-508.

Received November, 30, 2001 - Accepted March, 24, 2002

