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Markers for hepatitis A, B and C in methadone maintained patients: an unexpectedly high co-infection with silent hepatitis B

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Abstract

Aims—To determine the prevalence of hepatitis A, B and C viruses in patients attending a methadone maintenance clinic in New York City.

Design—Cross-sectional.

Setting—The Adult Services Clinic of Weill Cornell Medical College, an urban hospital-affiliated methadone program.

Participants—Former heroin addicted adults (n = 103) on methadone maintenance therapy.

Measurements—Markers for hepatitis A virus [HAV immunoglobulin M (IgM) and imunoglobulin G (IgG)], hepatitis B [hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb)] and hepatitis C virus (HCVAb). Serum alanine aminotransferase (ALT) and quantitative HCV RNA were also obtained. Qualitative detection of HBV DNA and HCV genotype were obtained in a subset of subjects.

Findings—More than 40% of subjects had markers for all three viruses. HCVAb was the most prevalent (83.5%), followed by HBcAb (65.0%), HAV IgG (46.1%) and HBsAb (41.1%). Hepatitis C RNA was detected in 70.6% of HCVAb positive subjects. While no subject had HBsAg, HBV DNA was detected in 26.4% of subjects who underwent this measure; all (n = 20) had HBcAb as their only HBV marker. The presence of HBV DNA did not influence ALT. Subjects with HCV RNA had higher ALTs than those without HCV RNA.

Conclusions—Most methadone-maintained subjects had at least one marker for viral hepatitis, with 41.8% having markers for HAV, HBV and HCV. A quarter of subjects had silent HBV infection, defined as the presence of HBV DNA in the absence of HBsAg. These subjects should be considered infectious and pose a public health risk.

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Keywords

Hepatitis B; hepatitis C; methadone maintenance; occult infection; viral hepatitis

INTRODUCTION

The transmission of infectious hepatitis through injection drug use (IDU) has been recognized for more than 50 years [1]. Early studies by our group and others showed that 85%–95% of untreated heroin addicts and heroin addicts entering methadone maintenance treatment (MMT) had at least one serological marker for the hepatitis B virus (HBV) [2–4]. With the discovery of the hepatitis C virus (HCV) and the subsequent development of serological testing, 60–98% of heroin addicts and patients in MMT were found to have markers for HCV infection [5–8]. We have reported previously that 60% of MMT patients have serological markers for both viruses [9]. While hepatitis A virus (HAV) infection is transmitted less frequently through IDU, outbreaks in IDUs have been reported and infection in the setting of HCV increases the chance of fulminant hepatic failure [10,11]. Recent reports from rural Germany and Los Angeles County, California found that approximately 30% of IDUs have markers for all three viruses [12,13].

Standard screening for viral hepatitis includes testing for serum antibodies. As HAV infection is generally a time-limited illness, the presence of HAV antibodies [HAV immunoglobulin G (IgG)] indicates a resolved infection with ongoing immunoprotection from re-infection. Because vaccination for HAV stimulates HAV IgG production, standard HAV screening cannot differentiate between past infection and prior immunization.

Standard screening for HCV detects an antibody (HCVAb) which indicates infection but cannot discriminate between resolved and ongoing infection. The presence of HCV RNA determines ongoing infection and is detected in approximately 75% of those who are HCVAb positive. Currently there is no vaccination for HCV.

Like HAV, HBV is generally a time-limited infection. Less than 5% of adults infected with HBV develop chronic infection, with a third of these experiencing serious HBV-related illness [14]. Screening for HBV includes tests for active infection [HBV surface antigen (HBsAg) and HBV core antibody immunoglobulin M (HBcAb IgM)] and immunity [HBV surface antibody, HBsAb and HBV core antibody IgG (HBcAb IgG)]. Vaccination against HBV induces HBsAb, whereas HBV infection may induce both HBsAb and HBcAb production. Therefore, the presence of surface antibody in the absence of core antibody generally indicates prior vaccination. HBV DNA is present during active infection (i.e. during positive test for HBsAg), but it is not measured routinely except in those who require monitoring for chronic HBV and those in a treatment regimen. Except for uncommon circumstances (see Discussion of silent HBV, below), patients with previous HBV infection who have developed immunity (i.e. negative HBsAg and positive HbsAb, with or without HBcAb) no longer have detectible HBV DNA.

Serologically silent (also referred to as occult or latent) HBV infection is defined by the presence of viral DNA in the absence of HBsAg [15]. Viral DNA is necessary for viral replication and therefore communicability. Most patients with silent HBV infection, however, are HBcAb IgG positive [16]. While there are multiple tests to screen for HBV, standard screening is limited mainly to a test for infection (HBsAg) and a test for immunity (HBsAb) [14], and general clinical settings do not, therefore, include HBcAb in their screening panel. It is possible, then, that standard HBV screening will miss an important clue (i.e. HBcAb) to silent HBV infection. This is of clinical importance, because sera from patients with silent HBV infection is infectious and these individuals should be viewed as

having ongoing HBV infection [17,18]. Although no large epidemiological studies of silent HBV infection have been reported, several small studies have found associations between silent HBV infection and poor immuno-competence, injection drug use and HCV infection [19–21].

The present study reports data on HAV, HBV, HCV and silent HBV infection in a cohort of former opiate addicts on MMT attending the Adult Services Clinic of New York Weill Cornell Medical Center in New York City.

METHODS

From November 2000 to September 2004, we conducted tests for serological markers for viral hepatitis in former opiate addicts attending the Adult Services Clinic of Weill Cornell Medical Center in New York City, an urban MMT program. Recruitment was performed face to face with patients by a research physician and nurse. Several group education sessions regarding viral hepatitis and the study were also offered to patients and clinical staff. Clinical staff could refer patients to daily office hours for further study information/participation. The only exclusion to study participation was an inability to provide informed consent. Studies commenced only upon approval of the appropriate review committees of the Rockefeller University and the Weill Cornell Medical College and were conducted in accord with the Helsinki Declaration of 1975, as revised in 1983.

After obtaining written informed consent, we tested 103 subjects for HAV antibody (HAVAb IgM and IgG), HBV surface antigen (HBsAg), HBV core antibody (HBcAb IgM and IgG), HBV surface antibody (HBsAb) and HCV-RNA (HCV RNA 3.0 bDNA IVD, lower limit of detection 2500 copies/ml; Bayer Diagnostics, Berkeley, CA, USA). Thirty-three subjects also provided separate consent specific to HIV antibody testing. Serum ALT (upper limit of normal 37 IU/ml) was also determined.

Due to budgetary limitations we were able to test only the first 79 consecutive subjects enrolled in the study for HBV-DNA with real-time polymerase chain reaction (PCR) (range of detection $1.0 \times 10^2 - 1.0 \times 10^9$ copies/ ml). This molecular beacon-based assay was developed and validated by one of the authors (L.Z.), correlates well with COBAS AMPLICOR HBV Monitor [22] and offers a wider range of detection than any single available commercial assay (combined range for several products: $2.0 \times 10^2 - 5.0 \times 10^9$) [23]. Silent HBV was defined as the presence of HBV DNA in the absence of HBsAg [15]. Except where noted above, all laboratory evaluations were performed at the clinical laboratories of Memorial Sloan-Kettering Cancer Center (New York, NY, USA).

Data on viral markers were missing in a variety of individuals, either because of inadequate specimen size to perform the test or due to failure to perform the test. Of the 103 participants, one subject had no HAV data, nine had no HBsAb data and one was missing HCV-RNA data. Two of the 79 subjects tested for HBV DNA had missing data. No subjects were tested for HBeAg, HBeAb or HDV.

RESULTS

The average clinical census during the study period was 210 subjects. In all, 103 subjects enrolled in the study. Sixty-seven per cent of subjects were male and the median age was 46 years [range 22–71; standard deviation (8.7]. Fifty-seven per cent were Caucasian, 11% African American, 29% Hispanic and 3% were of other or undisclosed ethnicity. The demographics of the study subjects did not differ from those of clinic patients who did not participate in the study.

None of the subjects in this study was positive for HBsAg. Table 1 shows the prevalence of antibody markers for HAV, HBV and HCV. Forty-six per cent (48 of 102) of the patients were HAV IgG positive (no subjects had HAV IgM). While the clinic did not provide vaccination against HAV, we do not have documentation of the number of subjects who may have received vaccination elsewhere. Seventy per cent ($n = 72$) of all subjects had at least one serological marker for hepatitis B virus (data on number of subjects receiving HBV vaccination are unavailable, although only seven subjects had HBsAb as the sole HBV marker). Ninety-one subjects had complete data sets available for all viral markers; of these, 41.8% ($n = 38$) had markers for all three viruses (Table 2). Antibodies to HIV were detected in three of the 33 tested subjects.

Hepatitis C viral RNA was detected in 70.6% of HCVAb positive subjects ($n = 86$). There was no relationship between HCV viral load and the number of serological markers for viral hepatitis (data not shown). HCV RNA (4470 copies/ml) was detected in an HCVAb negative subject who had undergone previous ablative chemotherapy for lymphoma. This subject was also negative for all other antibody markers of viral hepatitis despite describing a remote history of ‘serum hepatitis’. Due to budgetary constraints, only the first 43 HCV RNA positive subjects underwent genotyping. Thirty-two subjects had genotype 1, five subjects had genotype 2a, five subjects had genotype 2b and one subject had genotype 3.

Data on HBV-DNA are available for the first 77 subjects enrolled in the study (Table 3). Twenty-six per cent ($n = 20$) were HBV-DNA positive. All 20 subjects had anti-HBcAb as their only HBV marker. Five (8.7%) of the 57 HBV-DNA negative subjects had HBcAb as their only HBV marker. Sixty-five per cent and 59% of HBV-DNA positive and HBV-DNA negative subjects, respectively, were also HCV-RNA positive.

Testing for HIV was performed in 23 of the 77 subjects who were also tested for HBV DNA. Antibodies against HIV were detected in three of these subjects. Of the 17 subjects undergoing HIV testing who were HBV DNA negative, only one was HIV positive. Of the six subjects undergoing HIV testing who were HBV DNA positive, two were HIV positive.

In the 77 subjects with data available for both HCV RNA and HBV DNA, we used a 2 × 2 factorial design analysis of variance to investigate whether viral status influenced levels of serum ALT (Table 4). Levels of serum ALT were significantly higher in subjects with HCV RNA than those without HCV RNA ($F_{1,73} = 11.4$, $P < 0.01$). The presence of HBV DNA did not influence ALT levels, nor was there an interaction effect between HCV RNA and HBV DNA on levels of ALT.

DISCUSSION

The presence of serological markers for viral hepatitis is commonplace in injection drug users. This study found that 83.5% of former opiate addicts attending a single methadone maintenance clinic were HCVAb positive. This finding is consistent with several reports of similar populations throughout the world [24–27]. The presence of markers for HBV infection in 72.3% and of markers for both HBV and HCV in 68.2% of patients with complete data sets is also consistent with other reports [28,29]. Forty-two per cent of patients had markers for all three viruses, which is higher than the prevalence reported in two recent studies [12,13]. Interestingly, 41% of patients with markers for HBV had HBcAb as the only marker of HBV. While none of the 103 subjects were HBsAg positive, between 65% and 80% of HBcAb-only patients had silent HBV infection.

Injection drug use has been a known risk factor for viral hepatitis for more than 50 years and the high prevalence of viral hepatitis in methadone-maintained patients in particular has been documented for over 35 years. Few studies, however, have evaluated simultaneously

markers for HAV, HBV and HCV in IDUs. Reimer *et al.* recently published findings similar to ours in an IDU population entering an opiate detoxification program in rural Germany [13]. In that study, however, the presence of markers for all three viruses was 32.9% compared to 41.8% in this study. This difference may be related to the older age of our study population (mean 46 years versus 28 years). In fact, in Reimer's study older age was associated with greater prevalence of viral markers. In a previous report we also found that older age at time of entry into methadone maintenance was associated with an increased prevalence of HCV [7]. Prevalence for all three viruses in our study is also higher than that reported by Fisher *et al.* in a California IDU population with a mean age (46 years) similar to our group [12]. One explanation for these differences is that we measured multiple markers for HBV, whereas Fisher and Reimer tested for HBcAb only. This cannot, however, account completely for the difference as only one of our patients with markers for all three viruses had HBsAb as the only HBV marker.

Compared to previous studies of hepatitis markers in IDUs, our study has a relatively small sample size. Our results are strengthened by simultaneous measures of markers for HAV, HBV and HCV in a methadone-maintained population. Previous studies of all three markers have either had no representation of methadone-maintained patients or included relatively small numbers of methadone patients, but did not provide subset data on this population. Unlike previous reports of multiple hepatitis markers in IDUs or patients in methadone, we also tested for the presence of HCV-RNA and, in a subset of patients, HBV-DNA. An important finding, with major public health impact, of this additional approach was the high prevalence of silent HBV infection, manifest only by HBV DNA in the absence of HBsAg.

There are three main hypotheses to explain an isolated finding of HBcAb IgG alone. One possibility is that individuals may have recovered recently from an acute HBV infection and that the serum was analyzed during a time-period following the disappearance of HBsAg but prior to the appearance of HBsAb. This is unlikely, given the age of our patient population and their extensive drug use history prior to, and reduction in drug use following, entrance into methadone maintenance, which would lead us to expect that acute HBV infection occurred years prior to the testing performed in this study.

A second explanation is that HBcAb alone reflects distant HBV infection and the expression of HBsAb has since fallen below the level of assay detection. This hypothesis is attractive in an MMT population as heroin use suppresses natural killer cell activity, a crucial element in the immune response to HBV, and this suppression can take several years in MMT to normalize [30]. While this may be a possibility, past presence or undetectable levels of HBsAb would probably have neutralized any present HBV-DNA, thereby reducing the chances of finding HBV-DNA. Additionally, intercurrent illness (e.g. HIV and cancer) may also lead to diminished immunocompetence with reactivation of HBV; however, our population had a low prevalence of HIV.

The third hypothesis is that HBcAb alone is a sign of chronic HBV infection. The presence of HBV-DNA in 80% of our HBcAb-only patients makes this an attractive hypothesis. Additionally, a recent meta-analysis of several small studies of various populations who have isolated HBcAb supports this hypothesis [31].

The clinical significance of silent HBV itself is unknown. When found, levels of HBV-DNA in silent HBV are low (in fact, below the level of detection of standard commercial assays). In HBV, disease progression and the risk of developing hepatocellular carcinoma are related to HBV viral load with a less than 1% 10-year cumulative incidence of hepatocellular carcinoma in subjects with less than 300 copies/mL [32].

While IDU is a risk factor for HBV and HCV infections, and each can lead to chronic liver disease, the current study found that only HCV had a significant effect on ALT levels in co-infected subjects. Several reports, however, indicate that despite little effect of co-infection on ALT there is an increased prevalence of biopsy-proven liver disease in co-infected individuals [33–36]. In patients with chronic HCV infection, there are also a few reports that silent HBV co-infection lowers the response to standard interferon monotherapy and increases the incidence of hepatocellular carcinoma [36–38].

Our study is limited by the use of a highly sensitive qualitative, rather than quantitative, assay for HBV-DNA. Using a HBV-DNA assay similar to ours, Torbenson *et al.* found that none of 81 injection drug users with silent HBV had detectable HBV-DNA upon parallel testing with a less sensitive commercial assay (lower limit of detection 200 copies/ml) [39]. Together, the findings indicate that silent HBV infection in IDUs exists at a very low viral load and may not contribute to progression of HBV-related liver disease. Nevertheless, these patients should be considered infectious and, therefore, pose a public health risk, especially if not maintained on effective treatment for their opiate dependence.

There are some limitations to our findings. We had several instances of missing data or data available on only subsets of subjects. Missing data were random in occurrence, and subset data (i.e. HBV DNA and HCV genotype) were obtained in consecutive subjects, thereby reducing the likelihood of selection bias. We had limited acceptance of HIV testing, which reduced our ability to assess the influence of HIV serostatus on viral hepatitis. We also did not test for the presence of HBeAg or HBeAb, markers indicating status of viral replication. The presence of HBV DNA in itself, however, obviates this. Finally, our HBV DNA assay did not provide viral load, making it difficult to comment on the possible influence that levels of HBV DNA may have on extent of liver disease.

The clinical implications of this study require further research. Medications are available to treat HBV, but their role in treating the patient with silent HBV infection alone is generally thought unnecessary. It is unknown, however, whether treatment of silent HBV will reduce the more advanced liver pathology seen in patients co-infected with silent HBV and HCV. Finally, as the sustained viral response to current HCV regimens remains around 50%–60% and the side-effect profile of the medications used to treat HCV causes some patients to decline or stop treatment, the benefit of generally well-tolerated suppressive HBV therapies in HCV-infected patients with silent HBV co-infection should be investigated further.

While the clinical implications of the study require further investigation, it is clear that our results have important public health impact. Vaccination campaigns and patient education have reduced the incidence of HBV and screening for HBV has been the major lead-in to these efforts. Standard screening strategies, however, will not detect the potentially large population with silent HBV. Therefore, clinics that screen for HBV using HBsAg and HBsAb only may wish to consider adding an HBcAb test or replacing HBsAb testing with HBcAb. Clinics may also wish to increase their prevention efforts by providing on-site HBV vaccination, something we have shown previously to be possible within a MMT clinical setting [40]. Finally, patients with silent HBV are infectious and must be educated regarding modes of transmission and prevention.

In conclusion, viral hepatitis is highly prevalent in IDUs and IDU is the largest cause of new viral hepatitis infection. Addiction treatment facilities such as MMTs are therefore at the front line of disease detection and prevention, and awareness of silent HBV should be disseminated throughout the addiction community.

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Table 1

Prevalence of viral hepatitis markers.

HAV IgM	HAV IgG	HBsAg	HBsAb	HBcAb	HCVAb
n = 102	*n* = 102	*n* = 103	*n* = 95	*n* = 103	*n* = 103
0/102 = 0%	47/102 = 46.1%	0/103 = 0%	39/95 = 41.1%	67/103 = 65.0%	86/103 = 83.5%

HAV IgM: hepatitis A virus immunoglobulin M; HAV IgG: hepatitis A virus immunoglobulin G; HBsAg: HBV surface antigen; HBsAb: HBV surface antibody; HBcAb: hepatitis B core antibody; HCVAb: hepatitis C virus antibody.

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Table 2

Prevalence of viral hepatitis markers in a subset of subjects for whom complete data for all three viruses were available.

Viral markers	Subjects (n = 91)
None	11/91 = 12.1%
HAV only	0/91 = 0%
HBV only	1/91 = 1.1%
HCV only	10/91 = 11.0%
HAV + HBV only	3/91 = 3.3%
HAV + HCV only	4/91 = 4.4%
HBV + HCV only	24/91 = 26.4%
HAV + HBV + HCV	38/91 = 41.8%

HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus.

Table 3

Hepatitis B virus (HBV) marker status and HBV DNA.

	HBsAb$^-$ HBcAb$^-$	**HBsAb$^+$ HBcAb$^-$**	**HBsAb$^+$ HBcAb$^+$**	**HBsAb$^-$ HBcAb$^+$**
HBV-DNA+ (n = 20)	0	0	0	20
HBV-DNA− (n = 57)	17	6	24*	5*

* Five subjects excluded due to incomplete data.

HBsAb: HBV surface antibody; HBcAb: hepatitis B core antibody.

Table 4

Serum alanine aminotransferase levels by hepatitis B virus (HBV) DNA and HCV RNA status. Mean (standard deviation) values are given as IU/ml.

	HCV RNA^{+*}	**HCV RNA^{-}**
HBV DNA^{+}	*n* = 13 68.3 (55.0)	*n* = 7 32.3 (19.7)
HBV DNA^{-}	*n* = 34 71.2 (55.8)	*n* = 23 25.9 (12.2)

*Significant effect on ALT, P <0.01.

HBV: hepatitis B virus; HCV: hepatitis C.