The Impact of Hepatitis C Virus Infection on Methadone Maintenance Treatment

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Abstract

Hepatitis C virus infection is now recognized as a common and serious complication of injection drug use and will be encountered frequently in methadone maintenance patients. Approximately 1.8% of the United States population, or 3.9 million persons, are infected with hepatitis C virus. A majority of acute hepatitis C virus infections are associated with injection drug use, and 64–88% of injection drug users in seroprevalence studies have antibodies to hepatitis C. Hepatitis C virus infection is almost always chronic, and alcohol use increases the clinical severity. Therapy with interferon and ribavirin will induce long-term remission in up to 43% of patients with hepatitis C virus infection. Proper diagnosis and treatment of hepatitis C virus infection will be indicated for many patients in methadone programs and will require considerable resources.

Key Words: Hepatitis C, methadone; heroin, injection drug use, alcoholism, epidemiology.

METHADONE MAINTENANCE is the most effective method for achieving sustained remission of chronic opiate use (1). Almost all patients in methadone programs have been injection drug users, and as such have been at risk for numerous medical complications (2). In the 1990s, chronic hepatitis C virus (HCV) infection became increasingly recognized as a widely prevalent and potentially serious disease in injection drug users and methadone maintenance patients. This article reviews the features of HCV infection of greatest relevance to methadone maintenance patients and discusses the impact of increasing numbers of HCV-infected patients in methadone programs.

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Virology

Although the existence of HCV was well established in the 1970s, its identification in the late 1980s was possible only after newer techniques of molecular biology became available (3, 4). Our knowledge of the molecular structure and features of HCV has expanded rapidly(4, 5). One important feature of HCV is sequence heterogeneity, which is more prominent in certain regions of the genome, such as areas encoding the envelope proteins (5). Genetic variability in this RNA virus has been manifest as genotypes and quasispecies. Genotypes are major groups of HCV strains, of which six major types and more than 50 subtypes have been described (5, 6); these differ in prevalence in different geographic locations and may influence clinical manifestations and response to therapy. Quasispecies are a heterogeneous but closely related group of viral sequences. They may be extremely complex, with 19 unique sequences having been isolated from one single patient (7). Viruses such as HCV, which form quasispecies, can develop mutations within an infected individual which escape the host's immune response of neutralizing antibodies

and cytotoxic T cells (4, 5). Quasispecies thus contribute to the very high frequency of chronic infection in HCV and render many potential vaccines ineffective.

Epidemiology

HCV has now been recognized as a major public health problem in the United States and elsewhere (8, 9). It is estimated that 1.8% of the U.S. population, or 3.9 million persons, are infected with HCV (8). The number of newly acquired cases of HCV was stable during the 1980s, but declined by more than 80% in the first half of the 1990s. This decline has been associated with a marked decrease in new infections in injection drug users (8). Nevertheless, injection drug users still comprise the single largest risk group for HCV. In data from the period 1991–1995 (8), 43% of cases of acute HCV were injection drug users; another 16% had past injection drug use; and 5% snorted cocaine. Others had a low socio-economic status; only 1% had no identifiable risk factor. With approximately 8,000–10,000 deaths occurring each year from HCV-associated chronic liver disease, HCV is now the most common indication for liver transplantation (10). The death rate from HCV is expected to increase markedly over the next decade as the population of infected persons ages.

Most injection drug users will become infected with HCV (2). In recent seroprevalence studies (11, 12), 64–88% of such persons had antibody to HCV (anti-HCV). In one study, 73% of injection drug users and 4% of oral drug users were HCV seropositive (13). HCV infection is usually acquired early in the patients' drug injecting careers (14, 15). Among persons injecting for one year or less, 77% had anti-HCV (15). HCV may be acquired after only a few injections, as in the weekend "recreational" user. Anti-HCV was found in 94% of persons who had injected drugs for 10 years or longer (14) and in 98% of injection drug users with chronic liver disease (16). By the 1970s, HCV had become well established in populations of injection drug users in New York City (16) and Victoria, Australia (17). A variety of HCV genotypes have been described in injection drug users (2), with type 1 the most common in the United States (18).

Sexual transmission of HCV occurs infrequently (19), and sexual practices have not correlated significantly with HCV seroprevalence in injection drug users (14). However, HCV-positive persons infected with human immunodeficiency virus (HIV) are much more likely to transmit HCV to a sexual partner (20, 21).

Several studies have addressed the incidence of HCV in injection drug users. Among 142 such persons in Baltimore who were susceptible to HCV, 43 (30%) became HCV-positive during a 6.5-year follow-up (22). Over the 8-year study period (1988–1996), the overall incidence of HCV infection was 6.4 cases per 100 person-years. The HCV incidence rate declined significantly during the study, however, with a rate of 13.4 cases per 100 person-years in 1988–1990 but only 2.3 in 1991–1996. The authors suggest that this marked decline is due to a saturation of the at-risk population rather than a reduction in high-risk behavior (22). In their study, frequent drug use and needle sharing were associated with seroconversion to HCV. In an Australian study, the overall incidence of anti-HCV seroconversion among injection drug users was 10.7 cases per 100 person-years (23). A decline in incidence was also seen but was not significant. Some subpopulations of injection drug users in Australia, e.g., young male prison entrants, have had HCV incidence rates as high as 41 cases per 100 person-years, albeit this was only in a small sample (24).

Studies conducted in methadone maintenance programs have yielded results similar to those in the studies of injection drug users cited above. The seroprevalence of HCV in methadone patients ranges from 67–84% (25–28). HCV incidence rates in three studies of methadone programs were 11, 12, and 22 cases per 100 person-years, respectively (26–28). Lower seroconversion rates might have been expected in methadone programs, since methadone maintenance treatment effectively reduces and often eliminates heroin injection and thus should reduce virus transmission (1, 29). Crofts et al. (28) state that many of their methadone patients who seroconverted either had injected drugs while on methadone or had gaps in methadone treatment. Some early seroconverters were probably already infected with HCV at the time that they entered treatment. For others, the high prevalence and infectivity of HCV ensure that even occasional injection drug use can cause HCV infection. Other factors contributing to HCV seroconversion during methadone maintenance treatment include an inadequate methadone dose (30–32) and cocaine injection (14, 29).

Clinical Features

In two-thirds of patients, acute HCV infection is subclinical (33). Acute hepatitis C does not

differ from other forms of acute hepatitis, but is very infrequent (33). Some cases escape attention because anti-HCV is not detectable in the early stages and HCV-RNA is the only marker (34). HCV infection becomes chronic in at least 85% of patients (33), and most of these patients seek medical attention because of abnormal liver tests which are accompanied by few, if any symptoms. In chronic HCV infection, serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) often fluctuate and may vary from normal to abnormal (35). Among HCV-infected patients who were current or former injection drug users who had been seen during at least four office visits, ALT was persistently normal in 42%, persistently elevated in 15%, and intermittently elevated in 43% (35). Repeated determinations of AST and ALT are needed for clinical assessment. Levels of ALT and AST are generally lower in chronic HCV infection than in other forms of viral and nonviral hepatitis, and they poorly predict liver histology (36). Liver biopsy is needed to assess the severity of liver injury. Liver histology was found to be less severe in HCV resulting from injection drug use than from transfusions (37). A few patients with chronic HCV develop cirrhosis rapidly, but most progress slowly or not at all. Cirrhosis has been seen in 20–30% after a follow-up of 10–20 years (33). The natural history of chronic HCV after 30–40 years, as in the person who acquires HCV from injection drug use in the late teens or early 20s and then remains otherwise healthy for decades, is as yet unknown.

The disposition of many drugs, especially those metabolized by oxidative pathways, is altered in chronic liver disease. Methadone undergoes oxidative biotransformation in the liver (38), but is also stored in the liver and released into the blood in unchanged form (39). This storage and release of unchanged methadone from the liver provides for low but stable plasma levels which maintain the patient in a stable state without opiate withdrawal or oversedation. Studies of methadone disposition in moderate (40) and severe (41) chronic liver disease revealed that most pharmacokinetic parameters for methadone were similar to those in controls. The essentially normal disposition of methadone in liver cirrhosis, even when severe, is attributed to a balance between damage to hepatic drug-metabolizing systems and damage to the storage and release functions of the liver regarding methadone (41). The usual methadone dose can be continued in patients with stable chronic liver disease, including advanced cirrhosis. In acute liver disease or acute decompensation of chronic liver disease, close clinical observation for signs of narcotic overdose or withdrawal is mandatory. A modest alteration in methadone dose may be indicated in some patients.

HCV infection is diagnosed by second- or third-generation enzyme immunoassay (42). Confirmatory testing is not necessary in chronic liver disease, but is important if serum aminotransferases are normal. Measurement of quantitative HCV-RNA level is needed prior to starting antiviral therapy for HCV, and to assess response, quantitative or qualitative HCV-RNA should be measured at the end of treatment and several months after treatment is stopped.

Alcohol and Hepatitis C

Patients with alcoholic liver disease have been found to have an increased frequency of anti-HCV (2, 43–45). The frequency of anti-HCV, confirmed by supplemental assays, in alcoholic liver disease ranges from 8–45%; it is seven times higher in alcoholics than it is in the general population (43). Injection drug use has been the most common risk factor identified in alcoholics with HCV infection (46, 47). In some studies, most of the alcohol users with anti-HCV had injection drug use or had had transfusions (45, 48). In others, however, parenteral risk factors were not found (45, 49, 50), and the high prevalence of anti-HCV in alcoholics was not explained (43). Lower socio-economic status may be a factor in the latter group (8, 43).

In our studies from 1978–1983, prior to the identification of HCV, liver cirrhosis was found to be significantly associated with alcoholism and injection drug use (51, 52). Cirrhosis was also diagnosed frequently in patients under age 35 with both alcoholism and injection drug use, but not with either one alone (51). We hypothesized that the observed frequency of cirrhosis was caused by additive and possibly synergistic effects of alcohol and one or more hepatitis viruses on the liver. When data from these patients were reanalyzed in the light of anti-HCV determinations on sera which had been frozen, cirrhosis was found in 30 of 67 injection drug users (45%) with anti-HCV and current or former alcohol abuse, but in only one of 19 (5%) with anti-HCV and no alcohol abuse (16).

Since the availability of anti-HCV testing, many studies have shown that patients with alcoholism and HCV infection have more severe liver disease than those with only one of these factors (43, 45). Advanced alcoholic liver disease has

been reported at a younger age in subjects with HCV infection (46, 53). Habitual drinkers with HCV infection have been reported to have higher levels of HCV-RNA than non-habitual drinkers with HCV (54). In a recent study, weekly self-reported alcohol consumption in a group of predominantly low or moderate drinkers was highly correlated with serum HCV-RNA level and hepatic fibrosis (55). In another study, total lifetime alcohol consumption was found to be strongly associated with the presence of cirrhosis (56). Patients with cirrhosis were also found to have consumed more alcohol while HCV-infected than those without cirrhosis (56). Other reports have shown that patients with alcoholic liver disease and HCV have more severe liver histology (57, 58), progress more rapidly to cirrhosis (58), and have a higher mortality rate (57).

All of these data strongly suggest that alcohol consumption should be prohibited for patients with chronic HCV infection. Total abstinence is mandatory for HCV-infected individuals with current or former alcoholism problems, or those with cirrhosis or severe chronic hepatitis. Abstinence is also recommended for those with milder disease and no chemical dependency problems, since it is unknown whether there is any safe level of alcohol consumption for individuals with HCV infection.

Treatment

Standard antiviral therapy for chronic HCV infection consists of the combination of interferon alfa-2b given subcutaneously three times weekly and ribavirin given orally twice a day (59, 60). Sustained undetectability of HCV-RNA at 24 weeks after treatment with this regimen was seen in 38% of patients in an American study (59) and 43% in an international study (60); these results were significantly better than for those using interferon alone. In these studies, results of treatment with interferon and ribavirin were superior to treatment with interferon alone, even in the presence of factors associated with reduced response, such as genotype 1, low HCV-RNA level, and increased liver fibrosis. Both studies suggest that patients with genotype 1 are better when treated for 48 rather than 24 weeks. These findings suggest clinical utility for HCV genotyping. Patients who maintain normal ALT levels and undetectable HCV-RNA for six months after completing treatment are likely to remain in virologic remission (61) and not develop advanced cirrhosis (62).

Interferon side effects are generally tolerable, but serious depression and even suicides have occurred. Ribavirin causes reversible hemolytic anemia, which requires close monitoring. Both medications can cause numerous additional adverse reactions, with which treating physicians need to be familiar. Methadone maintenance patients tolerate interferon well, but data on ribavirin are not available yet.

Alcoholic patients (43) and patients with cirrhosis (63) had markedly reduced response rates to interferon alone, Further studies are needed to determine whether such patients have a reduced response to combined therapy with interferon and ribavirin. Preliminary data suggest that patients with cirrhosis will benefit most from a 48-week course of combination therapy (60).

Patients on methadone with end-stage cirrhosis have successfully undergone orthotopic liver transplantation. Transplant centers treating these patients should be familiar with appropriate pain management (2).

HCV-infected patients who subsequently acquire hepatitis A virus infection have a markedly increased risk of fulminant hepatic failure and death (64). Administration of hepatitis A vaccine to HCV patients who are susceptible to hepatitis A infection is therefore recommended.

Methadone-Related Issues

Methadone maintenance treatment has been used for the treatment of opiate addiction for more than 35 years and has proven to be safe even when administered for 15 years or longer (65). Methadone therapy is also associated with normalization of cellular immunity which had become abnormal during injection drug use (66). As already noted, methadone maintenance may be safely continued in the presence of stable chronic liver disease (40, 41). Therefore, it is appropriate to continue methadone maintenance treatment over years or decades, in patients with chronic HCV infection.

Injection drug users not infected with HCV, who enter a methadone program and do not use other drugs or alcohol, are very likely to remain HCV-negative. Expansion of methadone maintenance treatment would undoubtedly prevent some new cases of HCV infection. However, it is likely that the high seroprevalance of anti-HCV in injection drug users, coupled with the ability of HCV to be transmitted by small numbers of injections, will result in ongoing seroconversions to HCV, as suggested by the studies cited above (26–28). Further research in this area is needed. Methadone maintenance treatment should be available to any chronic injection drug user who

desires this treatment (67, 68). Many studies have shown that higher doses of methadone lead to less ongoing heroin use during treatment and to greater treatment retention (30–32). Use of optimal doses of methadone should reduce the risk of seroconversion to HCV during treatment.

It is certain that methadone programs will contain large numbers of patients with all stages of HCV infection. Those with chronic hepatitis or early cirrhosis will need to be considered for antiviral therapy. Evaluating and treating large numbers of currently untreated patients will require considerable resources. Methadone maintenance programs should identify physicians in the community with an interest in treating HCV infection. It may be advantageous for some patients to receive hepatitis C treatment at the methadone clinic; a similar recommendation has already been made for antiretroviral therapy for HIV (69). It is reasonable to require methadone maintenance patients to abstain from alcohol and substance use before starting antiviral therapy, given the need for close clinical monitoring and the poor response seen in patients drinking alcohol (43). Also, patients with mild, stable, chronic HCV may do well with observation and no antiviral treatment (70).

New therapies, such as protease inhibitors, will probably become available in the 2000s. New antiviral agents will need to be assessed for interactions with methadone (38), as has now been reported for HIV protease inhibitors (71). Longer-acting interferon preparations administered once-weekly may be useful for patients who should not be given needles. Methadone maintenance patients with end-stage cirrhosis due to HCV should be considered for liver transplantation. Those who are not candidates for this procedure due to age, co-morbid medical conditions, poor social support, or ongoing alcohol or drug use will require supportive care.

In summary, HCV infection is one of many challenges which must be met in the process of providing quality medical care to methadone maintenance patients. Given the current incidence and prevalence data cited above, HCV infection is expected to remain a problem. Further research in the virology, epidemiology, treatment, and prevention of HCV infection is essential if better outcomes are to be achieved.

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